ANNUAL REVIEW OF MEDICINE

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VOLUME 10

1959

ANNUAL REVIEWS, INC.
PALO ALTO, CALIFORNIA, U S A.

ANNUAL REVIEWS, INC.
PALO ALTO, CALIFORNIA, U.S.A.

Library of Congress Catalog Card Number. A51-1659

FOREIGN AGENCY
Maruzen Company, Limited
6 Tori-Nichome Nihonbashi
Tokyo

PRINTED AND BOUND IN THE UNITED STATES OF AMERICA BY
GEORGE BANTA COMPANY, INC.

PREFACE

In each year of its decade of publication, the *Annual Review of Medicine* has presented the views of outstanding workers concerning recent important developments in the various medical areas in which they are respectively expert Over two hundred syntheses of current thought in the most active fields of medicine have thus appeared. While admittedly adding to the huge bulk of general medical literature, these volumes have also contributed to that rather smaller and more choice body of writing which concerns itself with the formulation of views through the sifting rather than the gathering of information. We do not regard these efforts as perfect, but are pleased with their progress, and try annually to improve their helpfulness. The cooperation of the authors of this tenth volume of the *Review* is hereby acknowledged gratefully, as is that of Miss Beryl Daniel, Editorial Assistant.

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VOLUME 11 (IN PREPARATION)

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INFECTIOUS DISEASES
(SOME ASPECTS OF SALMONELLOSIS)[1]

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The first description of *Salmonella* was published by Salmon & Smith in 1886 (1), and in 1888 Gärtner recognized the role of the members of this genus in epidemic gastroenteritis (2). During the ensuing 70 years, several thousand reports have been published on the bacteriology, epidemiology, treatment, and prevention of salmonellosis. Despite this voluminous literature, neither prophylaxis in nor therapy for these afflictions can be said to have attained a satisfactory state. Indeed, with the exception of typhoid, diseases produced by *Salmonella* appear to be increasing in incidence.

It is the purpose of this article to summarize certain information about *Salmonella* infections other than typhoid, emphasizing those aspects which seem important in the clinical recognition and management of disease produced by these organisms It has been necessary to omit several topics such as the discovery of new species of *Salmonella* and the complex subject of identification and classification by antigenic analysis

The discussion to follow centers around sources of infection and modes of transmission of these organisms, factors of importance in man's susceptibility to infection by *Salmonella*, and evaluation of therapy.

Epidemiology

Knowledge of the epidemiology of salmonellosis is, in large measure, confined to intestinal infection caused by these bacilli. Sporadic systemic infections may possibly arise by entry of the organisms into the body through routes other than the gastrointestinal tract, but definite evidence that this occurs with any regularity is almost wholly lacking.

The basic importance of the fecal-oral route in sporadic cases and the role of contaminated food in outbreaks of *Salmonella* gastroenteritis are obvious and well known. However, in contrast to the typhoid bacillus and most of the dysentery bacilli whose habitat is almost exclusively the human intestine, there are enormous reservoirs of *Salmonella* in lower animals and a consequently larger potential for human infection Gradual appreciation of the multiplicity of the sources of *Salmonella* in nature has led to recognition of many previously unknown chains of transmission and cycles of cross-infection, and has also pointed up the need for revision and extension of control measures.

Incidence of human disease.—While the number of reported cases of

[1] In the preparation of this review, emphasis has been placed upon publications issued between January, 1955 and July, 1958 but, in many instances, references to earlier reports have been necessary for amplifying or clarifying discussion.

salmonellosis undoubtedly represents only a fraction of its true prevalence (3), examination of available figures shows that *Salmonella* infections other than typhoid have increased strikingly. Typical is the experience of MacCready, Reardon & Saphra (4) who found in Massachusetts a sevenfold increase in reported cases of salmonellosis between 1950 and 1956. A summary of data for the entire United States by Edwards (5) indicated a steady decline in typhoid between 1945 and 1955 and a sevenfold increase in other *Salmonella* infections for the same period. Savage (6) is of the opinion that the increase in salmonellosis in Great Britain is out of proportion to improvements in diagnosis and reporting. However, it cannot be stated unequivocally at present that the observed increases signify anything more than better detection and more efficient recording. It is clear, nonetheless, that salmonellosis is a health problem of considerable magnitude.

Edwards (5) has recently commented upon the apparent disproportion between the number of outbreaks of staphylococcal food poisoning in the United States and that in Great Britain. Whereas the annual totals show the staphylococcus to be 4.5 times as frequent as *Salmonella* in the etiology of food poisoning in the United States, *Salmonella* is three times as common as the staphylococcus in the British figures. Discounting the idea that the British pay little attention to staphylococcal poisoning, Edwards points out that on a per capita basis this type of disease is actually reported twice as frequently in England as in the United States. Similarly interpreted, the figures show that salmonellosis is 28 times more frequent in Britain than in this country! Edwards' conclusion that salmonellosis is probably a far greater problem in the United States than reported incidence would indicate seems wholly justified, particularly since it has been shown so clearly that a part of Britain's *Salmonella* problem arises from importation of American egg-powder (7 to 10)

Reservoirs in lower animals.—Most physicians are familiar with the generalization that *Salmonella* organisms are found in lower animals; several reviews on this subject are available (5, 11 to 15). The true extent of the ubiquity of the bacteria of this group in nature is almost unbelievable. Not only are the so-called host-adapted strains of *Salmonella* which are peculiar to a given animal species often capable of producing disease in man, but it is also well established that nonhost-adapted strains from human or other sources can be harbored and disseminated by an animal not naturally parasitized by them (5, 15).

That these reservoirs are of major epidemiologic importance has been shown clearly in studies demonstrating close correlation between the *Salmonella* species predominating in animals and those isolated from human disease in many localities including the United States (42), Africa (43), Canada (44, 45), and Australia (46, 47).

Probably the greatest single source of human disease is poultry, including chickens, ducks, and turkeys. Some idea of the relative frequency of salmonellosis in domestic animals can be gained from the experience of Bruner & Moran who collected data on 69 outbreaks in cattle, 1056 in swine, and 4658 in poultry (49).

Human carriers.—The incidence of asymptomatic carriers of *Salmonella* in the general population is about 0.2 per cent (6, 50). As might be expected, among cultures submitted to typing laboratories and hence representing a selected group, the proportion from asymptomatic individuals is high, varying from 15 per cent (50) to more than 20 per cent (4, 11). For reasons to be discussed shortly, the carrier rate among food handlers and certain other occupational groups is higher than that in the general population. The report by Galton & Hardy (51) stating that 63 per cent of the cultures typed in their laboratory came from well carriers was undoubtedly weighted by the predominance of food handlers in their subjects (5).

There is no question about the fact that asymptomatic intestinal infection can follow contact with clinical cases or ingestion of contaminated food (52 to 57), and that recovery from illness is often followed by the carrier state in infants and adults (54 to 59). In contrast to the tendency for adults to cease shedding organisms within a few weeks, infants are likely to remain carriers for many months (54, 55, 56). The mechanisms involved in the carrier state for *Salmonella* are not clear. It is certain that the gallbladder is not the focus of survival with anything like the frequency that applies in typhoid (60). This is in accord with the observation that permanent carriers of *Salmonella* other than *S typhosa* are exceedingly uncommon (4). The longer duration of the carrier state in infants has been attributed to differences in intestinal flora, etc., but nothing definite has been established The studies made by Thomson (61, 164) have shown that the numbers of bacteria excreted by carriers often exceed those in symptomatic infections and leave no doubt about the importance of carriers in the spread of disease. Infection with multiple types of *Salmonella* is undoubtedly much more common in man than heretofore realized (88, 152) Juenker (62) studied 75 patients in the Michigan State Health Department, using exhaustive bacteriologic techniques, and found that 13 were shedding more than one *Salmonella* species, the stool of one individual containing no less than seven different serotypes

Modes of transmission.—The importance of proper sewerage and waste disposal is no less for salmonellosis than for other enteric infections (63, 64) and requires no elaboration.

Almost any food product of animal origin is a potential source of human infection, and the problem of contamination in food-processing has gained

prominence as large-scale commercial enterprise in this area has grown (5, 6, 15, 65 to 68, 90). Infection in cattle, for example, can lead to dissemination of organisms in milk (17, 20) or in beef (69). More important, the infection can be passed to other animals. The environment of abbatoirs is inevitably contaminated with resulting infection of meat from previously well animals during processing.

Galton *et al.* (21) found that the incidence of positive stool cultures for *Salmonella* in swine rose from 7 per cent on farms to 25 per cent in the holding pens at slaughter houses. This demonstration that meat-packing plants are also stations for the collection and concentration of *Salmonella* makes it less surprising that the carrier rate for these organisms should be higher among abbatoir workers.

As already mentioned, the poultry industry is another source of difficulty. If fowl are not already infected, contamination is almost inevitable in processing plants (29). Furthermore, the difficulties of controlling infection in eggs which arise from pooling for drying or freezing are a classic example of the epidemiologic problems that have arisen from commercial processing (6, 9, 10, 70, 71) Even chicks sold at Easter may spread salmonellosis (30).

Contamination of fresh fish (72), smoked fish (73), canned fish (67), yeast (74), coconuts (75), almost every conceivable type of meat, fresh or processed (67), and even watermelon (76), either through spread from animals or human carriers during some stage of the voyage to the market have all been noted.

The *Salmonella* bacilli are hardy organisms, capable of long survival under conditions which are less than ideal. Solowey & Calesnick found that organisms in eggs can survive cooking by boiling in the shell, frying, or scrambling (79), and *Salmonella* bacilli were cultured periodically for two years from a sample of dried beef, "biltong," containing 10 to 12 per cent NaCl (69). Postive cultures were obtained from samples of rat feces held at room temperature for 21 weeks (80)

Not the least of the problems in controlling contamination of the wide variety of foods that are common sources of *Salmonella* is the need for new sampling and testing techniques (77). Screening tests for coliform bacteria such as those that have become standard in milk and water bacteriology cannot be applied meaningfully to other products, and much additional work is needed to clarify methodology in this field (77).

A final and extremely important source of *Salmonella* infection encompasses the numerous by-products of the meat-packing industry and includes bone meal, fertilizers, domestic animal feeds, fish meal, etc. (81) Walker (82) cultured 123 samples of organic fertilizers and found *Salmonella* in 40 per cent. Of bone meals cultured, 70 per cent were positive and, *in all*, no less than 34 different *Salmonella* serotypes were isolated. While it is doubtful that growing plants would take up pathogenic bacteria (81), the possibilities for mechanical contamination of produce are numerous, and occupational exposure to these materials probably involves an increased carrier rate al-

though no studies on this point have been carried out. Fish meal, a component of many fertilizers and feeds, is an abundant source of *Salmonella* bacilli (83); Edwards (5) mentions the experience of Rohde who isolated ten different species of *Salmonella* from a single sample of this substance! Surveys of commercial feeds (14, 66, 84, 85) confirm the fact that these products are of major importance in perpetuating and extending the reservoirs of animal salmonellosis. For example, Hardy & Galton (66) in Florida found that 27 per cent of 98 samples of dog meal contained *Salmonella*, with positive cultures obtained from feeds manufactured by nine of the eleven firms whose products were tested.

Resistance and Susceptibility to Salmonellosis

In the typical, circumscribed outbreak of salmonellosis, clinical illness does not occur in every individual known to be at risk. Some become symptomatic and may continue to show positive stool cultures after recovery, others harbor the organism but remain asymptomatic, and still others remain clinically and bacteriologically negative (52, 88, 89). Attack rates for clinical illness are higher in infants than in adults (53, 54, 55). Some *Salmonella* species are consistently associated with severer illness than are others (50, 78, 91), but no matter what is the infecting species in a large outbreak, there results a spectrum of disease ranging from transient discomfort to rapidly fatal illness (50, 90, 91) Without discounting the importance of dosage in some instances, it is obvious that the explanation for these variations in response requires a consideration of the infected host as well as the infecting organism

It is often stated (50, 90 to 93) that mortality from salmonellosis is greater in infants and the aged and that many severe or fatal cases are associated with pre-existing debilitating disease. On the basis of 174 fatal cases, Saphra (91) computed mortality rates of 5 8 per cent in infants, 2.0 per cent between ages one to fifty, and 15 per cent in patients over fifty In the oldest group, at least one-third had another disease such as arteriosclerosis, hypertension, diabetes, or cancer In a series of 95 hospitalized patients with salmonellosis, Eisenberg, Palazzolo & Flippin (92) reported coexisting disease in 74 per cent of adults and 27 per cent of children but did not elaborate further There is nothing surprising in these observations on morbidity and mortality at the extremes of life or in the presence of another disease. These generalizations apply to many infections and are in no way unique or peculiar to salmonellosis.

Experimental investigations of host resistance to *Salmonella* infections have usually followed the general pattern of such studies with other infecting agents. The susceptibility of animals is influenced by genetic factors (94, 95), nutrition (94, 96 to 100), ionizing radiation (95, 101), adrenal steroid hormones (102), various metabolic inhibitors (103, 104, 105), altitude stress (106, 220), wetting agents (107), and bacterial endotoxins (108). These findings constitute important additions to the study of re-

sistance, but none can be said to be peculiar to salmonellosis and their significance in human infection by *Salmonella* is unknown.

Close examination of published reports, however, reveals several situations in which human susceptibility to salmonellosis, especially systemic infections, is influenced in a fashion that seems almost specific. In addition, several peculiarities of infection in man by *Salmonella* have been observed with enough frequency that it seems worthwhile to draw attention to them.

Gastrointestinal infection.—It is postulated frequently that normal intestinal bacteria protect against invading pathogens by nutritional competition, elaboration of antibiotic substances, etc. Miller and his associates (109 to 112) found that a single dose of streptomycin enhanced the susceptibility of mice to oral *Salmonella* infection by nearly one hundred thousand times Normal resistance was restored promptly by feeding fecal suspensions and re-establishing the bacterial population of the gut. Meynell (113) has confirmed these findings completely. The role of antibiotics in the pathogenesis of staphylococcal enterocolitis has received a great deal of attention in recent years (114, 115, 116), the possibility that a similar mechanism may operate in salmonellosis is strongly suggested by the patient reported by Finger & Wood (117) in whom oxytetracyline activated *Salmonella* enteritis. However, at the present time, *Salmonella* enteritis has not been recognized as a frequent complication of the administration of antibiotics to man.

The susceptibility of patients convalescent from gastrointestinal surgery to *Salmonella* enteritis was pointed out by Friedemann in 1938 (118), and several examples of postoperative salmonellosis were reported by Waddell & Kunz in 1956 (119) The latter authors suggest that a change in microflora or the occurrence of achlorhydria after gastric surgery may lower resistance The studies of Meynell (113) suggest that in mice the stomach is a relatively inefficient barrier to the entry of virulent *Salmonella*

While it is now clear that antibiotics alone can produce staphylococcal enterocolitis, the risk is greater when these drugs are given to patients after gastrointestinal surgery (120) and it is probable, although not certain, that surgery alone can lead to the disease (120, 121, 122). Whatever the responsible mechanisms may prove to be, it is safe to conclude that diarrhea in a post-operative patient who is receiving antibiotics, or with other evidence of pre-existing bowel dysfunction, should not be labelled "nonspecific" until proper bacteriological investigations have been carried out. It is conceivable that minor, day-to-day variations in the intestinal flora of individuals might be of great significance in determining attack rates in epidemics of salmonellosis, but this is speculation at present.

A study conducted by Coetzee & Pretorius (123) among African children with kwashiorkor may be relevant. Stool cultures obtained from 106 cases and 69 controls showed an equal incidence of *Salmonella* and *Shigella* infections in the two groups Kwashiorkor is accompanied by severe malnutrition and diarrhea, neither of which appeared to influence resistance to

enteric pathogens in this instance. Similar investigations are greatly needed.

Systemic infections.—*Salmonella* bacteremia has been described as a complication of parturition (20, 124), streptococcal pharyngitis (125, 126), measles (127), chickenpox (128), leukemia (129–134), beriberi (135), lupus erythematosus (136), and many other acute and chronic diseases in which secondary bacterial infection is not unexpected. Indeed, the only unusual feature of most of these sporadic cases has been the finding of a *Salmonella* as the causative organism rather than some more common bacterium. Because the combination of salmonellosis with the many diseases in this group seems better explained by coincidence rather than any specific relationship, they will not be discussed in any further detail.

Malaria.—*Salmonella* bacteremia has been described as a complication of malaria by many observers. Not only do epidemics of systemic salmonellosis coincide with malarial outbreaks, but the severity of the bacterial infection is notably greater in malarial patients (137). *Salmonella* sepsis has been such a frequent complication of malarial treatment of neurosyphilis (138) that the routine use of a vaccine against *S. enteritidis* was once considered for patients who were to be given therapeutic malaria (139). In addition to the association of these two infections, evidence for the reduction in resistance to salmonellosis by malaria comes from the frequently reported observation that control of malarial paroxysms with quinine is followed by spontaneous amelioration and subsidence of the *Salmonella* bacteremia (137, 140) The susceptibility of patients with malaria to salmonellosis is apparently not widely appreciated. For example, Baker & Bragdon (141) reported six cases of systemic *S enteritidis* infection among troops stationed in New Guinea without referring to the role of malaria, although at least five of their patients had had malaria with parasitemia prior to the onset of *Salmonella* infection

Relapsing fever.—The frequency with which *Salmonella* bacteremia complicates severe cases of louse-borne relapsing fever is well known (142 to 146, 153) Chung & Chang (142) observed 337 patients with relapsing fever of whom 15 had positive blood cultures for *Salmonella*. Of 11 fatal cases of relapsing fever autopsied by Anderson & Zimmerman in Korea (144), five had complicating *Salmonella* bacteremia. While the suggestion has been made that both infections are transmitted by the louse, and *Salmonella* organisms have been cultured from lice (39, 146), Anderson & Zimmerman found no evidence for this mode of transmission in their patients. The frequent occurrence of these infections in the same patient could, of course, represent simultaneous inoculation of organisms by the vector, but the occasional finding of shigellosis and relapsing fever together (142, 144) lends support to the idea that relapsing fever is accompanied by a lessened resistance to enteric pathogens, especially *Salmonella*.

Bartonellosis.—Of the several diseases in which secondary salmonellosis is likely to occur, none is more striking than bartonellosis or Carrión's disease (147, 148, 149). According to Cuadra (149), Barton isolated a ba-

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gestive evidence that other hemoglobinopathies share in this (173, 174). In reviewing a series of 36 consecutive cases of sickle-cell anemia, Hook and his associates (172) found four patients with *Salmonella* bacteremia, complicated by osteomyelitis in three. Several suggestions have been made to account for the systemic susceptibility to invasion by *Salmonella*. These include severe anemia, debility, "autosplenectomy," capillary thromboses in the intestine, etc., and there is no firm evidence for a dominant role of any one of them It is altogether probable, however, that sickle-cell disease impairs resistance to salmonellosis in a highly specific manner. Bacteremic infections in patients with leukemia, aplastic anemia, or other pancytopenias are extremely frequent and involve the *Staphylococcus*, coliform bacteria, *Proteus*, *Pseudomonas*, and, occasionally, *Salmonella*, thus providing evidence of a "general" susceptibility to infection In patients with sickle-cell disease, however, bacteremia produced by organisms other than *Salmonella* is unusual. A review of blood dyscrasias complicated by bacteremia at the Johns Hopkins Hospital in recent years bears out this statement. The majority of bacteremias in patients with sickle-cell disease were produced by *Salmonella* organisms, whereas no less than eight different Gram-negative bacilli were involved in the infections encountered in the patients with leukemia, aplastic anemia, and other pancytopenias (175).

The frequency of osteomyelitis is probably attributable to the localization of organisms in the areas of ischemia and necrosis of bone so common in sickle-cell anemia, and is but one example of the striking tendency of *Salmonella* bacilli to initiate local infection in diseased tissue of any type. This is discussed in more detail in the following section.

Localized infections.—Frequent mention has been made of invasion by *Salmonella* bacilli of tissues that are the site of pre-existing disease (50, 176) This is not exclusively a property of *Salmonella*, of course; other bacteria such as *Pseudomonas*, *Proteus*, and *Staphylococcus aureus* have a notorious affinity for injured tissues. However, a review of reported instances of abscess formation in the course of systemic salmonellosis reveals so many extraordinary examples of localization in foci of other disease that a brief compilation of some of them is justified

In reviewing the records of 59 patients with *Salmonella* osteomyelitis, Saphra (50) stated that trauma occasionally seemed to "trigger" the infection but did not give details. The predilection of *Salmonella* bacilli for bone in sickle-cell anemia has been mentioned already A case of osteomyelitis described by Schein (177) is interesting A mild diarrheal illness in an elderly woman was followed by fever and severe pain in the thigh, and operation revealed an abscess containing *S. typhimurium* at the site of a healed fracture of the femur which had been fixed with a metal plate 3½ years previously. A most curious syndrome produced by the invasion of bone is the combination of vertebral osteomyelitis and aortic aneurysm. This was reported in one of 86 sporadic cases of *Salmonella* infection reviewed by Angrist & Mollov (160), and in one of three patients described by Simon &

cillus from the spleens in five cases of acute bartonellosis in 1898, and for several years before his final discovery of the *Bartonella* thought that this bacillus was the causative agent. The organism isolated by Barton was probably a *Salmonella*, he called it "bacilos semiltificos" because it resembled the typhoid bacillus so closely.

The high mortality in acute bartonellosis or Oroya fever is almost entirely accounted for by secondary salmonellosis, and the "effectiveness" of chloramphenicol in Oroya fever is attributable to its action against this secondary infection rather than the *Bartonella* organisms (147, 148, 149). The incidence of salmonellosis in Cuadra's series of patients with Oroya fever was 40 per cent (149); of 8 patients treated with choramphenicol, all recovered, and of 5 untreated, all died. Cuadra (149) reviews the evidence from several careful studies, and comes to the conclusion that immunity to salmonellosis is "specifically" lost during the hemolytic phase of Oroya fever and that this is not a reflection of some general depression of resistance to all types of pathogenic bacteria

Liver disease.—The close association of epidemics of jaundice and of salmonellosis has been noted repeatedly through the years since the report of Barker & Sladen in 1909 (150). During World War I, *Salmonella* organisms were isolated from stools or blood of icteric patients so frequently that it was concluded by many that these bacilli were the etiologic agents of hepatitis (151, 155), and this idea persisted for many years. Havens & Wenner (155) observed *S. choleraesuis* bacteremia in two volunteers inoculated with infectious hepatitis virus, and their article reviews thoroughly the relationship between these two diseases. It must be admitted that salmonellosis is likely to occur in the same conditions of sanitation that favor the spread of viral hepatitis (63, 155), and that this factor alone would lead to frequent double infections The great number of instances in which there is bacteremia, however, lends substantial support to the hypothesis that the viral infection depresses resistance to salmonellosis (155)

Patients with hepatic cirrhosis are prone to blood stream invasion by enteric Gram-negative bacilli (156, 157), and it is not surprising that a number of cases of *Salmonella* bacteremia complicating chronic liver disease have been described in the medical literature (158, 159, 160). There is nothing to suggest that these represent anything more than the general lowering of resistance to enteric organisms in cirrhosis, and the mechanisms involved are unknown (161)

There are occasional reports of salmonellosis complicating leptospirosis (162, 163), but information is too scant to allow definite conclusions about the frequency of this association

Sickle-cell anemia.—In 1951, Hodges & Holt (165) pointed out that the incidence of *Salmonella* osteomyelitis was increased in patients with sickle-cell anemia. Once attention had been directed to this association, many additional publications appeared (166 to 172), and it has become apparent that salmonellosis is a relatively common complication of sickling, there is sug-

infants are generally less resistant to meningeal infection than older children and adults, and that *Salmonella* meningitis is particularly likely to occur in the very young age group

Finally, the frequency with which *Salmonella* meningitis complicates syphilitic involvement of the meninges (192) and meningococcal meningitis (192, 196 to 200) is worth mentioning. In any patient with meningococcal infection who appears to "relapse," secondary infection by *Salmonella* should be considered and ruled out.

Summary remarks.—In the vast majority of the disorders mentioned in the above discussion, increased susceptibility to salmonellosis is probably nothing more than a reflection of a general depression of resistance to infection. However, in a few diseases, there is strong evidence to indicate a specific predisposition to infection by *Salmonella* which far exceeds any general susceptibility to other bacterial species. These include *malaria, relapsing fever, bartonellosis, viral hepatitis,* and *sickle-cell anemia.* It is probable that other hemoglobinopathies will eventually be included in this group. A great deal more information is needed before any conclusion can be drawn about hepatic cirrhosis and leptospirosis

Icterus is frequent in all of these disorders Severe impairment of liver function occurs in hepatitis and relapsing fever, and hemolysis and anemia characterize malaria, bartonellosis, and sickle-cell disease.

Without speculating upon the mechanisms of decreased resistance which may be common to these diseases, it can safely be stated that further clinical observations are greatly needed and that experimental investigations can profitably be directed toward the role of hemolysis, liver injury, icterus, etc , in resistance to salmonellosis.

Therapy

Because so many definitive studies of the action of antimicrobial drugs against *Salmonella* have been conducted using the typhoid bacillus or patients with typhoid, any discussion of the treatment of salmonellosis must draw heavily upon them Despite certain differences in pathogenesis, there is enough similarity in the problems involved in the therapy of typhoid and other salmonelloses that it is possible to draw certain broad conclusions from these investigations

Sensitivity to antibiotics.—There is a puzzling disparity between the results of *in vitro* tests of sensitivity of *Salmonella* bacilli to antibiotics and the effectiveness of antimicrobial drugs *in vivo.* Streptomycin, chlortetracycline, and chloramphenicol may inhibit growth of these organisms in the test tube, but chloramphenicol is notably more effective than the others in the treatment of salmonellosis (201, 202, 203). Werner *et al* (203) found that chlortetracycline and chloramphenicol at the same serum levels exerted comparable bacteriostatic effects upon typhoid bacilli encased in agar discs and implanted intraperitoneally. However, significantly larger dosages of chlortetracycline were required to achieve proper serum levels, and it may well be

Silver (178). Single cases have also been reported by Dehlinger (179), Miller (180), and by Talbot & Hunt (222). There can be little doubt that erosion of the vertebral bodies by the dilated aorta is the "trauma" responsible for localizing the infection. It is probable that this sequence of events is relatively common if one judges by the striking similarity of these cases from the literature.

Abscess formation in hematomas (176) occurs occasionally, and an area of infarction may be the focus of persistent *Salmonella* infection. This is sometimes of therapeutic importance as, for instance, in a case reported by De La Torre (181) concerning an infant with unilateral thrombosis of a renal vein and persistent *Salmonella* bacteremia in whom nephrectomy achieved a complete cure.

Some idea of the frequency with which localization of the bacilli at a site of trauma occurs can be gained from the experience of Giglioli (137) in British Guiana. This author treated a number of patients for malaria and *Salmonella* bacteremia with quinine, resulting in amelioration of both diseases as has been mentioned in a previous section. He observed especially dramatic improvement in one patient given quinine dihydrochloride intramuscularly by mistake. This patient's improvement seemed to coincide with the development of a *Salmonella* abscess at the site of the injection. This observation led Giglioli to test intramuscular quinine dihydrochloride in the treatment of 59 cases of salmonellosis without malaria. Of these, 20 developed abscesses at an injection site!

Not only may patients with various tumors develop a complicating *Salmonella* infection, but the neoplastic tissue itself is often the focus of persistent infection. Reports of this type are numerous; they include localization in retention cysts of the kidney (137), corpus luteum cyst (182), ovarian cysts (183, 184), uterine myomata (185), carcinoma (176, 186, 187), and pheochromocytoma (188) It is obvious that the occurrence of *Salmonella* bacteremia in any patient with a neoplasm should direct attention to the tumor as a possible source of infection

Other examples of localized salmonellosis include infection of the thyroid gland in exophthalmic goiter (189), development of abscesses in the subcutaneous nodules of onchocerciasis (190), and persistence of the urinary carrier state in patients with coexisting bilharziasis (191)

Meningitis.—About three-fourths of the reported cases of *Salmonella* meningitis have occurred among children under two years of age, and the peak incidence occurs under the age of 3 months (192, 193) Meningitis is a common cause of fatalities in nursery outbreaks of salmonellosis and, in a number of epidemics in newborns, a large proportion of the infections have been meningeal (56, 194). Ziai & Haggerty (195) have reviewed the various mechanisms which may account for the susceptibility of newborns to all types of meningitis, including increased permeability of the blood-brain barrier, trauma at birth, and several immunologic factors. It is fair to say that no single explanation seems to fit all cases. It is clear, however, that

day & McEacharn (227) used randomized controls in a group of infants treated with chloramphenicol for *Salmonella* gastroenteritis, and found no differences in the clinical and bacteriologic course of the disease between 25 treated babies and 26 untreated controls.

Systemic infections.—Chloramphenicol is clearly the drug of choice in typhoid and paratyphoid (228, 231, 236, 241, 247), bacteremias (149), and localized infections of bones or joints (166, 172, 222, 223, 224, 229, 230), meninges (225), lungs and pleura (93, 229, 253), and other sites (158, 226). The clinical response is usually not dramatic; improvement ordinarily begins within 48 hr. but often 4 to 6 days are required for defervescence under the best of circumstances Therapy with chloramphenicol occasionally precipitates a Herxheimerlike reaction in patients with typhoid and paratyphoid (247).

Chloramphenicol is bacteriostatic only and persistence of organisms in tissues and exudates is common. *Salmonella* bacilli isolated during relapses are ordinarily sensitive to chloramphenicol, and clinical responses to second or third courses of the drug differ in no appreciable way from the first. Mortality is high in infants, the aged, and patients with underlying disease (50, 92, 204), in endocarditis (50), and in meningitis (50, 192, 244) despite antibiotics.

Therapy with chloramphenicol in bacteremic salmonellosis, including typhoid, should probably be continued for a minimum of 14 days. Smadel, Bailey & Lewthwaite (241) found higher relapse rates in typhoid patients given chloramphenicol for 8 days or less than in those in whom no treatment was given; they observed no relapses in a group of 31 patients treated for a minimum of 14 days Intermittent administration of the antibiotic and its combination with typhoid vaccine have both been said to reduce relapse rates (231, 248)

When chloramphenicol elicits no response in systemic salmonellosis, tetracyclines (202, 251), penicillin (210, 232), streptomycin (206), or polymyxin (232) can be tried.

Chronic carriers—It is difficult to evaluate many reports of the use of antibiotics in the treatment of *Salmonella* carriers because authors have failed to define the carrier state The period of excretion of bacilli after intestinal infection is highly variable (55, 89, 154, 204). Shedding of organisms is likely to cease spontaneously during the first year after infection but remissions after that time are rare (4, 252). While antibiotics are usually ineffective in chronic carriers (50, 212, 213, 235, 251, 252), occasional successes have been reported with tetracyclines (235), chloramphenicol (208), chloramphenicol combined with typhoid vaccine (246), penicillin (252), and neomycin (245). Cholecystectomy is indicated in carriers with gallbladder disease (212, 233, 234) if excretion persists for more than a year.

Other measures—Cortisone or other adrenal steroids given along with chloramphenicol ameliorates symptoms of typhoid and paratyphoid more rapidly than the antibiotic alone (228, 236). Cortisone (221, 237) or acetyl-

that the differences in drug effectiveness in salmonellosis involve "drug-host" rather than "drug-parasite" relationships.

Virtually all strains of *Salmonella* are inhibited by concentrations of chloramphenicol that are well within the range of serum levels obtained in man by giving conventional doses of the drug (90, 204 to 208, 249, 250), most requiring less than 5.0 µgm per ml. (205, 208, 227, 249, 250). Many strains are also sensitive to tetracyclines, streptomycin, neomycin, and polymyxin B

Although *Salmonella* bacilli are "resistant" to penicillin, this can be overcome in many instances by increasing the concentration of the antibiotic According to Welch & Lewis (209), the multiplication of three-fifths of *Salmonella* strains is prevented by a concentration of 10 units per ml. of penicillin. Rabe (210) tested seven different *Salmonella* serotypes and found all were inhibited by 16 units per ml., a concentration readily obtained by parenteral administration of 150,000 units/kg., per day of penicillin, together with oral probenecid There is no relationship between *Salmonella* serotype and susceptibility to antibiotic action (204).

Resistance to antibiotics.—Resistance to chloramphenicol can be induced by repeated passage in media containing increasing concentrations of the drug (249), but emergence of resistant strains during therapy is unusual. Organisms that persist in feces, blood, bile, or pus during treatment are, as a rule, as sensitive to chloramphenicol as they were before therapy was instituted (211, 212, 213, 250) Exceptions have been recorded; Greenspan & Feinberg (214) isolated a chloramphenicol-sensitive strain of *S. tennessee* from the blood of a patient before treatment and, after six weeks of chloramphenicol, a resistant strain was found in the patient's stool culture. There have been occasional instances of the development of chloramphenicol resistance during treatment of typhoid (215)

There is no evidence for any increase in chloramphenicol-resistant strains of *Salmonella* in the years since introduction of this drug This is not the case with tetracyclines Huey & Edwards (205) tested the sensitivity to antibiotics of 200 strains isolated from animals or man before 1948, and that of 200 strains collected since that date All were sensitive to chloramphenicol and there was no change in the proportion of cultures resistant to streptomycin. All of the older strains were inhibited by 3 1 µgm. of tetracycline per ml., but among the recent cultures 9 per cent from fowls and 5 per cent from man grew in 50 to 100 µgm per ml This increase in tetracycline-resistant strains may be related to the widespread practice of adding tetracyclines to animal feeds.

Gastroenteritis.—Despite contrary reports (54, 210, 219), there is no good evidence that antimicrobial drugs exert a beneficial action upon *Salmonella* gastroenteritis in man. There is no shortening of illness and the length of time that organisms persist in the intestinal tract is unaffected (90, 204, 206, 216, 217, 218, 227) It is clear that evaluation of treatment in an acute, self-limiting disease requires the use of adequate controls. Macdonald, Fri-

day & McEacharn (227) used randomized controls in a group of infants treated with chloramphenicol for *Salmonella* gastroenteritis, and found no differences in the clinical and bacteriologic course of the disease between 25 treated babies and 26 untreated controls.

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Other measures.—Cortisone or other adrenal steroids given along with chloramphenicol ameliorates symptoms of typhoid and paratyphoid more rapidly than the antibiotic alone (228, 236). Cortisone (221, 237) or acetyl-

salicylic acid (238) can produce transient hypotension and hypothermia and it is probably advisable to reserve their use for severely toxemic patients only.

Pooled human gamma globulin is alleged to exert a synergistic effect with chloramphenicol in salmonellosis of mice (239). Waisbren (240) used gamma globulin along with antibiotics in the treatment of an assortment of patients, one of whom had *Salmonella* osteomyelitis, but it is impossible to draw any conclusions from his results because there were no controls.

The importance of surgery in the management of intestinal perforations (242) and in the drainage of abscesses deserves mention. Wound infection is an occasional late complication of surgical intervention in systemic salmonellosis (243).

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GASTROENTEROLOGY[1]

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ESOPHAGUS

Physiology.—Studies of the gastroesophageal junction and the esophageal vestibule of Lerche, by means of cineradiography and pressure measurements on 10 healthy medical students, indicate the presence of a physiologic sphincteric mechanism at the cardioesophageal junction which opens earlier on drinking than on swallowing (1, 2). When 20 to 40 ml. of barium were held in the mouth for one or two minutes and then swallowed, the substance was retained in the gastroesophageal junction for approximately 1.4 sec. before passing into the stomach (1) When the same amount of barium was drunk immediately, the material passed without delay through the junction.

Cardiospasm.—Cardiospasm may be produced in cats by the injection of a 5 per cent solution of phenic acid between the two layers of smooth muscle lining the wall of the cardia which destroys the ganglion cells of Auerbach's plexus (3). Similarly, in Chagas' disease the intramural nerve plexus of the esophagus is found to be destroyed by the neurotoxin released from the dead parasites, producing megaesophagus (4) In cardiospasm, the primary peristaltic wave of deglutition is replaced by feeble, nonpropulsive contractions The resting tonus of the gastroesophageal sphincter is normal but this area fails to relax with deglutition (5); the action of the sphincter at the pharyngoesophageal junction is normal Dilatation of the inferior esophageal sphincter by aerostatic or hydrostatic dilators or by esophagomyotomy does not restore the normal esophageal motility but, by one or another of these means, the resting pressures at the sphincter as measured by electromagnetic pressure transducers, are restored towards normal (6). A residual sphincter, important in preventing reflux, has been demonstrated. While not relaxing with swallowing, it yields more readily to the intraesophageal pressure developing during deglutition Flood *et al.* found that the propulsive responsiveness of the esophagus to distention diminished in achalasia but was not lost completely, suggesting that impairment of the intramural neurogenic mechanisms is partial rather than total (7) Longitudinal muscle strips taken from the lower end of the esophagus at operation from patients with or without achalasia, behave pharmacologically as smooth muscle, with a neurogenic mechanism involving cholinesterase (8) The histologic appearance varied, but approximately normal numbers of ganglion cells were noted in two of seven samples taken from patients with achalasia,

[1] The survey of the literature pertaining to this review was completed in June, 1958.

suggesting that the increased tonus of the lower esophageal segment is related also to abnormal function of the main portion of the esophagus, rather than exclusively to an alteration at the cardia.

Spasm.—In diffuse spasm the esophagus is distorted, a situation often described as "curling" Most patients are in the older age groups; there may be no symptoms, or only intermittent dysphagia and retrosternal discomfort. In 16 patients treated for this condition, normal peristalsis was present in the upper portion of the esophagus, but in the lower segment, the peristaltic wave of deglutition pressure was replaced by a simultaneous and prolonged rise in pressure (9). The upper and lower esophageal sphincters relaxed normally on swallowing and the response of the esophagus to methacholine chloride also was normal

Hiatus hernia and esophagitis—The etiologic factors in hiatus hernia include a congenital "predisposition" or hiatal weakness and degenerative changes in the musculature surrounding the esophageal hiatus (10). In a study of fresh cadavers, the significant muscles about the hiatus were found to originate from the right crus of the diaphragm; the phreno-esophageal membrane or ligament did not appear to be an important anatomic structure in this group (11) In a series of 115 infants and children studied at necropsy, the gastroesophageal region was characterized by a small, powerful hiatus, with pronounced crural overlap, a formidable phrenoesophageal membrane and secure fixation of a narrow terminal esophagus (12). Increased intraperitoneal pressure contributes significantly to the muscle-weakening preceding hiatus hernia and also to the associated gastroesophageal regurgitation Intraperitoneal pressure, as reflected by intragastric pressure measurements with a strain-gauge manometer attached to an indwelling polyethylene tube, increased with posture, respiration, coughing, straining, and external compression produced by corsets, obesity, pregnancy, air-swallowing, over-eating, and abdominal tumors (13). Regular and cineroentgenography may demonstrate notches or a static ring at the distal margin of the esophageal vestibule when it is herniated and distended; since these notches denote the junction between the esophageal vestibule and the stomach, their presence above the diaphragm is indicative of a hiatus hernia (14) In addition to relaxation of the cardiac sphincter mechanism in hiatus hernia, neuromuscular imbalance of the entire esophagus may be present (15) Reflux of acid gastric contents is the cause of the esophagitis, but it is not an invariable occurrence (16) The tonus of the physiologic cardioesophageal sphincter is highly important in preventing reflux Simultaneous recordings of intraluminal pressure and pH at various levels within the esophagus and stomach disclosed acid regurgitation in 54 of 90 patients, esophagitis was demonstrable in 52 of the 54 individuals (17). The digestive action of HCl and pepsin is responsible for the esophagitis developing under such circumstances Deep penetrating ulcer developed when the esophagus of dogs was bathed in unaltered gastric juice (18) Exposure to gastric juice mixed with duodenal contents or to the latter alone, resulted

in a superficial esophagitis. Contact of the esophagus with jejunal or colonic contents produced minimal or no changes. The anomaly in which the lower esophagus is lined with columnar epithelium may be complicated by reflux esophagitis, stricture, and chronic peptic ulcer, as well as by carcinoma (19). The junction between the squamous and the columnar epithelia usually is 20 to 25 cm. from the incisor teeth

Carcinoma. Boyd and his co-workers have found that supervoltage irradiation may be a useful adjunct to surgery in the management of carcinoma of the esophagus, providing palliation of symptoms and retarding the progress of the neoplasm (20). Cobalt 60 irradiation, given in doses of 3000 r in two and one-half weeks for palliation and 6000 r in five weeks for curative effects, produced partial or temporary restoration of swallowing in patients treated for esophageal carcinoma Eight of 41 patients survived for periods exceeding two years, according to Mustard (21).

STOMACH-DUODENUM

Gastric secretion and absorption.—Acid secretion and oxygen uptake by frog gastric mucosa continued, but at reduced rates, when the sodium in the bathing solution was 0 6 m*M*. or less; both reached maximal levels when the sodium was increased to 10 m*M*. (22). The secretion was 75 per cent of maximum when lithium replaced sodium, was unaffected when chloride was replaced by bromide, but diminished when the replacement was iodide. These and other data indicate that the essential process in gastric acid secretion is the production of HCl.

Hogben *et al.* (23) have reported in recent experiments that the human stomach is capable of absorbing most acidic and weak basic drugs at rates comparable to or more rapid than its absorption of ethyl alcohol Salicylic acid, thiopental sodium, secobarbital sodium, and antipyrine, undissociated in the acid gastric contents, are absorbed readily; whereas completely ionized drugs, including dihydrochloride, *l*-ephedrine, and aminopyrine, are not absorbed. These results are in accord with the hypothesis that the human gastric mucosa functions as a lipoid barrier, selectively permitting the passive diffusion of nonionized lipide-soluble compounds Similar observations were made by Schanker *et al.* for the small intestine of the rat (24)

Experimental inhibition of gastric secretion—Baugh *et al.*, in working with dogs with vagus-denervated Heidenhain pouches, learned that excision of the antral musculature and replacement with colon musculature decreases gastric secretion. Transplantation of this hybrid antrum (antrum mucosa and colon musculature) into the colon as a diverticulum, restores secretion in the Heidenhain pouch toward normal. Isolated pouches constructed from the hybrid antrum respond to gastric secretory stimulants. Their observations indicate that the musculature of the antrum is not necessary for the formation and release of gastrin, whereas the mucosa and submucosa are essential The gastrin cell may be a nerve cell, perhaps located in Meissner's plexus (25). Severing the nerve plexus in the submu-

cosa of the antrum significantly reduces acid secretion from gastric antral pouches, suggesting that the antrum is an independent neurohormonal structure (26).

Pancreatic secretion, given intravenously to dogs with Heidenhain pouches (27) not only stimulates pancreatic secretion but, according to observations by Greenlee *et al*, also reduces the output of acid. Oberhelman *et al.* report that secretin does not inhibit the response to vagal stimulation or to histamine, but prevents the gastric secretory response to gastrin which suggests a mechanism whereby acid food in the duodenum inhibits gastric secretion. The increased gastric secretion after excluding the gastric antrum from contact with food (28), or after resection of the antrum [Ragins *et al.* (29)] suggests the elaboration of an inhibitory substance from the antral mucosa on contact with HCl (29). Similarly, in dogs with Heidenhain pouches and separate marsupialized antral pouches, Jordan (30) has observed *reduction in pH within one antral pouch usually inhibits production* of HCl by the Heidenhain pouch when stimulated by histamine given intravenously or by alcohol perfusion of the second antral pouch. The vagi do not appear to be essential for the inhibiting effect Similar studies elsewhere, on the other hand, are interpreted to indicate that acid brought in contact with the antral mucosa prevents the formation or release of gastrin, rather than producing an inhibitory hormone (31) Other investigators, supporting the concept of an inhibitory humoral factor from the antrum, emphasize this mechanism as an advantage of segmental gastric resection in the surgical treatment of duodenal ulcer(32)

Anderson and his co-workers devised methods for the exclusion of the antrum and duodenum from the normal gastrointestinal passage and observed increased gastric secretion in dogs with Pavlov pouches (33). The response to histamine also is augmented and is unaffected by antrum resection, probably because of the removal of an inhibitory mechanism in the duodenum The duodenal mechanism for inhibiting gastric secretion in dogs apparently includes two components one, receptivity to changes in pH and *mediated neurogenically, and, sensitivity to changes in osmolarity,* mediated humorally Receptors for both mechanisms appear to be confined to the duodenum (34). In contrast to the animal observations, the gastric secretory responses to histamine, insulin, and gruel, measured before and at intervals up to six months after resection of the gastric antrum, pylorus, and first part of the duodenum in patients with duodenal or pyloric ulcer and hypersecretion, did not diminish during the early postoperative period (35). The *subsequent decrease in acid secretion, without corresponding reduction in* pepsin, paralleled the development of gastritis, as demonstrated by gastric biopsy The data suggest that either no important role is played by the gastrin mechanism in human gastric secretion or no gastrin is liberated from the body of the stomach or first portion of the duodenum. The presence of a potent inhibitor of gastric secretion in Heidenhain pouch dogs has been confirmed (36). Normal human gastric content also possesses secretory in-

hibitory properties which are independent of the action of saliva. This finding is of considerable potential importance since, in other experiments, repeated injections of an inhibitory substance extracted from the gastric content suppressed acid secretion and produced atrophic changes in the gastric mucosa of dogs (37).

Gastric secretion in man.—Studies made by Schayer & Ivy (38) on rats utilizing C^{14}-1-histidine are interpreted as indicating that the secretion of HCl following feeding is mediated by histamine. In patients with active peptic ulcer, however, the blood histamine is within the normal range and is not correlated with basal secretion of HCl (39). According to Friedman *et al* (40), histamine not only stimulates the parietal cells but also promotes the active secretion of pepsin from the chief cells. Decreased gastric secretion, including diminished responsiveness to histamine, has been observed previously during states of withdrawal and during sleep in an infant with depression and gastric fistula. However, during sleep in healthy subjects the gastric response to histamine remains high, suggesting a biological difference between sleep in normal persons and the sleep-withdrawal state in certain depressive conditions [Cohen *et al.* (41)]. In patients with duodenal ulcer, the sustained gastric secretory response to insulin-hypoglycemia is considered to have two components: an early (vagal) phase and a delayed (pituitary-adrenal) phase; the vagal component usually is the more pronounced (42). In nonulcer individuals, the response may be of the sustained duodenal ulcer type, or unsustained, but dominated by the vagal phase. Complete vagotomy in patients with duodenal ulcer usually abolishes both responses; the delayed phase persists in a small percentage of cases. The studies are interpreted as indicating synergism between vagal and pituitary-adrenal functions in the cephalic phase of gastric secretion.

Pepsinogen—With a polyethylene cannula inserted in a gastrosplenic vein, blood pepsinogen can be measured in dogs under conditions obviating the important role of the kidneys. Peptic secretagogues, methacholine bromide, and ACTH increase pepsinogen in the gastric venous blood but not in the peripheral circulation according to reports by Earle & Hoar (43). The blood pepsinogen also is not elevated consistently in dogs subjected to various ulcer-producing surgical preparations In other studies (44) sham feeding, ACTH, and bethanechol chloride increased gastric acidity and pepsin, but not the blood pepsinogen, urinary pepsinogen also did not rise, as might have been anticipated if there were a renal mechanism regulating blood pepsinogen at a constant level (44). In man, serum and urinary pepsinogen usually are higher in patients with duodenal ulcer than in normal persons, and are higher in men than women, however, wide individual variations limit the usefulness of single analysis of urinary pepsinogen (45). Furthermore, as Segal *et al* (46) have found, serum and urinary pepsinogen may be elevated despite apparently low outputs of HCl and gastric pepsin, and urinary pepsinogen may not be demonstrable in acid secretors. Measurements of proteolytic activity of gastric juice, and of urine at pH 1.5 and 3 5,

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indicate that gastric pepsin and gastric cathepsin are two distinct enzymes, secreted and excreted at different rates (47).

Adrenal steroids, peptic ulcer, gastric secretion.—Among a group of patients with rheumatoid arthritis, Kern and his co-workers have reported that the incidence of peptic ulcer was higher than usual and progressed further during treatment with adrenocortical hormones or phenylbutazone (48). In another series of 117 patients treated with corticosteroids, studied by Kammerer *et al.* (49), ulcers developed in 36 patients (31 per cent); 31 of the 36 ulcers were gastric in location. If hypersecretion were involved, a much higher proportion of duodenal ulcers should have occurred. The absence of a rise in gastric secretion in healthy volunteers given hydrocortisone, prednisone, and prednisolone for two weeks suggested decreased tissue resistance, rather than hypersecretion, as the decisive factor (49). Lambling (50) found additional evidence of the development of numerous gastric lesions in patients with various diseases given prednisone, and the course of gastric ulcers produced by thermocautery in rats given cortisone [Skoryna *et al.* (51)] also was attributed to the tissue-damaging effects of steroids. Cortisone and ACTH seemed not to interfere with the replacement of mucous epithelium in gastric pouches following chemical desquamation with eugenol, according to the work of Janowitz and his colleagues (52), whereas the healing of excisional ulcers in gastric explants was retarded but not inhibited completely. Since, in previous experiments, cortisone failed to elicit even minute amounts of HCl in dogs with Heidenhain pouches, the decisive factor probably was decreased tissue resistance.

The effect of 8-hr. infusions of ACTH, hydrocortisone, prednisolone, and aldosterone upon the volume, acid, pepsin, and viscosity of gastric juice, and simultaneous measurements of blood and urinary pepsinogen were compared with the results of injection of the vehicle alone and with a 4-hr. infusion of histamine in normal men (53). The hormones did not alter acid or pepsin outputs significantly except for a rise during the administration of aldosterone. The viscosity of gastric juice was reduced significantly by ACTH and by corticosterone, but not by hydrocortisone. ACTH increased the output of urinary pepsinogen while the plasma pepsinogen was unchanged, the increase being attributed to enhanced renal clearance of pepsinogen (54) These results were reproduced by hydrocortisone and, to a much smaller extent by corticosterone, while aldosterone had the opposite effect. Measurements of adrenocortical function in the basal state and after stimulation with ACTH intravenously, did not disclose significant differences between patients with duodenal or gastric ulcer and control subjects (55) Normal plasma corticosterone and cortisol levels and normal responses to a standard intravenous ACTH stimulus also were observed in patients with duodenal ulcer and with benign gastric ulcers, the results in the two groups were similar (56). These observations, therefore, do not support the concept of adrenocortical hyperactivity in peptic ulcer.

Drug-induced peptic ulcer.—In addition to ACTH and adrenal steroids, Kirsner has found that the administration of numerous therapeutic agents, especially salicylates and phenylbutazone, may be complicated by the development or reactivation of peptic ulcer, with hemorrhage and perforation (57). The mechanisms involved are not understood completely, but they include stimulation of gastric secretion and decreased resistance of the gastroduodenal mucosa. In addition, Lange reports that salicylates are important causes of gastric hemorrhage, especially in older persons taking medication for long periods (58). In six of 10 patients given 0 6 gm. acetylsalicylic acid, gross blood appeared promptly in the gastric content (59). An acute gastritis with multiple erosions was demonstrable in 12 patients treated by Lamphier & Young, with upper gastrointestinal hemorrhage secondary to the ingestion of aspirin (60). The taking of salicylates after meals and in coated tablets may decrease the tendency to gastric irritation according to Lange (61). Large doses of reserpine given orally (exceeding 1 mg. daily) and small amounts injected intravenously are capable of stimulating gastric secretion (62). West (63) reports five cases of peptic ulcer produced by the same drug. Studies conducted by Rider *et al.* (64) using anticholinergic drugs suggested a peripheral site of action and possible mediation locally by serotonin. However, the serotonin precursor, 5-hydroxytryptophan (5HTP) inhibited, rather than augmented, the spontaneous, insulin-induced and urecholine-induced gastric secretion; the response to histamine was uninfluenced (65) Iproniazid (Marsilid), which increases the serotonin in the brain by inhibiting the action of monamine oxidase, and 5HTP each significantly lowered gastric secretion in the cat (66).

Blood groups—The increased incidence of blood group O in patients with duodenal ulcer and blood group A in patients with gastric carcinoma has been reaffirmed by Weiser (67); however, the validity and significance of this interesting observation are not yet apparent and current observations do not resolve the problem It is suggested that certain mucopolysaccharides containing the blood group substances may exert a protective influence upon the gastrointestinal mucosa (68, 69) In another study conducted by Balme & Jennings, blood group O predominated in patients with carcinoma of the body of the stomach, whereas group A was more frequent among individuals with carcinoma of the antrum (70) The distribution for gastric ulcer was similar· group A for ulcers of the antrum and group O for ulcers above the angulus of the stomach

Duodenal ulcer.—Gastric hypersecretion is an important predisposing factor in the pathogenesis of duodenal ulcer but it is not the only determinant Three parameters appear to be involved, a physiologic component determining the susceptibility of the duodenum to ulceration, a psychologic parameter defining the relatively specific conflict-inducing psychic tension, and a social factor establishing the environmental event ultimately precipitating the combined effects of all parameters. The increased antidiu-

retic activity in the blood of patients with duodenal ulcer suggests that pituitrin stimulates the parasympathetic center in the hypothalamus, with resultant gastric hypersecretion and hypermotility (71).

Peptic ulcers with pancreatic tumors—Patients with recurrent peptic ulcerations of the duodenum and jejunum, resistant to medical and surgical therapy, occasionally have noninsulin-producing, presumably alpha cell, tumors of the pancreas and tremendous gastric hypersecretion (72, 73). A relationship to polyglandular neoplasms is indicated in the coexistence of tumors of the hypophysis or the adrenal cortex. Since glucagon is secreted by pancreatic islet alpha cells resembling the tumor type, glucagon has been implicated in the gastric hypersecretion. However, crystalline glucagon, in single doses of 10 or 20 μg. given intravenously or intramuscularly, inhibited insulin and meal-stimulated gastric secretion in dogs (74, 75) and in man, indicating that this compound is unimportant in the genesis of peptic ulcer (76).

Surgical treatment-physiologic aspects—The assumption that subtotal gastric resection produces achlorhydria is not necessarily correct, for the usual tests may not demonstrate low concentrations of HCl More precise measurements of pH, the response to secretory stimulants, and blockade of intestinal reflux, permitting more accurate collections, indicate the presence of acid, at least in the early postoperative stage, according to a report by Van Geertruyden (77). The subsequent achlorhydria is attributed to the prolonged action of alkaline duodenal content upon the gastric mucosa, causing atrophy of the parietal cells. Gastric juice from most untreated patients with duodenal ulcer digests the esophagus of the cat during a 2-hr. perfusion, whereas less than 10 per cent of gastric specimens from nonulcer patients demonstrate this effect. Studies in patients operated upon for duodenal ulcer by various techniques, indicate that the substantial segmental resection affords the greatest protection in terms of decreased digestive capacity of the gastric content (78)

The reported incidence of the dumping syndrome after subtotal gastric resection varies from 2 to 45 per cent, depending upon the definition of dumping and the accuracy of the history; at least 5 per cent and possibly up to 15 per cent of the patients may require treatment. The syndrome apparently is caused by rapid filling of the jejunum with hypertonic foods, large amounts of fluid are secreted by the jejunum to restore the isotonicity of the chyme, thereby lowering the plasma volume After gastric resection there may be incomplete absorption of ingested protein (79). In dogs, the increased excretion of fat in the feces parallels the extent of resection of the acid-secreting portion of the stomach (80) Deficient digestion of fat, rather than defective absorption, is the cause of postgastrectomy steatorrhea, and may be lessened by the oral administration of processed raw pancreas and bile salts (81). Prolonged steatorrhea after gastric resection or gastroenterostomy, with malabsorption of vitamin D and calcium, may lead to ostemalacia (82). Nutritional therapy after gastrectomy requires sustained

dietary supervision, and protein anabolic agents (83); frequent feedings, avoidance of excess carbohydrates and of fluids with meals, postprandial recumbency, antispasmodics, potassium salts and occasionally, psychotherapy (84, 85). Impaired absorption of vitamin B_{12} after subtotal gastrectomy is unusual but can occur. The uptake of B_{12} was normal in patients in whom the fundus and mid-portion of the stomach had been removed (proximal gastrectomy), indicating that intrinsic factor was produced by the remaining distal portion of the stomach (86). In one patient, described by MacLean, with defective absorption of Co^{60} B_{12}, histologic examination of the resected stomach demonstrated chronic inflammation and gastric atrophy (87). The physiological and mechanical problems accompanying gastric resection are much less common after vagotomy and gastroenterostomy (88). The procedure of vagotomy and antral exclusion lowered the gastric secretion of 50 patients with duodenal ulcer treated by Waddell & Bartlett (89). The clinical results were favorable; none of the patients was incapacitated although diarrhea, mild dumping, and weight loss occurred occasionally

Gastric ulcer—The clinical similarities between benign and malignant small gastric ulcers have encouraged resection of all gastric ulcers, regardless of diagnosis, according to Comfort & Priestley (90). However, thorough and skillful diagnostic study permits accurate differentiation in the vast majority of cases (91, 92) In a series of 307 patients reported by Doll *et al.* (93) with ulcers classified as benign, the diagnosis was established at operation in 22 requiring surgery for hemorrhage or perforation, in 266, on the basis of clinical evidence, and, in 19, the possibility of malignancy was not excluded completely Three years later, the diagnosis was changed to carcinoma in only one of the 226 patients of group II and in only four of the suspect group III Among 47 patients with bleeding gastric ulcer treated medically by Arias and his group, hemorrhage recurred in only three during the subsequent four to eight years (94)

Gastric carcinoma.—Carcinoma of the stomach is the most frequent neoplasm in Japan The incidence of gastric carcinoma, on the basis of an approximately 8-yr. survey, thus far has not increased among individuals exposed to the atomic bomb at Hiroshima (95) In a large series of patients with gastric carcinoma observed during the years 1932 to 1954 in the United States, the surgical mortality declined from 27 to 5 7 per cent, the 5-yr. survival rate has risen from 15 to 37 per cent, and the 10-yr rate from 7 to 16 per cent [Marshall (96)]. Screening for achlorhydria and hypochlorhydria is an effective means of diagnosing gastric cancer in the asymptomatic phase The incidence of gastric cancer in the achlorhydria-hypochlorhydria group is 4 5 times greater and in the pernicious anemia group 22 times higher than in the same segment of the normal population (97) Studies made during 1957–58 indicate that the development of exfoliative cytology of the stomach provides another important method for the recognition of gastric malignancy (98, 99, 100)

SMALL INTESTINE

Carcinoid tumors.—The principal clinical features of functioning carcinoid tumors include diarrhea, episodes of flushing, a heart murmur, "asthma," and abnormal amounts of 5-hydroxy-indole acetic acid (5HIAA) in the urine. The cutaneous flush may persist for as long as 30 min. but usually is transient; cyanosis may persist and telangiectases develop Histologically, the affected skin is characterized by dilation and congestion of veins and capillaries, occasional vascular thickening, edema, and chronic inflammation (101, 102). In one case reported by Bridges *et al.*, a pronounced skin lesion, indistinguishable from pellagrous dermatitis, responded to nicotinic acid (103). There is no direct correlation between the flushing and the quantity of 5HIAA in the urine The output of 5HIAA is not reduced by chlorpromazine hydrochloride, but may be increased by histamine. Increased outputs of histamine in the urine, and elevated blood levels of 5-hydroxytryptamine (5HTP), also are demonstrable in patients with carcinoids (104). According to investigations made by Sjoerdsma *et al.*, the abnormal chemical changes may disappear after complete removal of the tumor. The tumor mass, rate of serotonin turnover, and the tumor pool of serotonin can be estimated by measuring the amount and radioactivity of 5HIAA after the administration of radioactive 5-hydroxytryptophan (105). The low fasting plasma tryptophan and low urinary N^1-methylnicotinamide levels suggest a disorder of tryptophan metabolism. There also may be a distinct group of carcinoid tumors producing 5-hydroxytryptophan rather than 5-hydroxytryptamine [Sandler & Snow (106)].

Five-hydroxytryptamine usually increases the tonus of the intact human small intestine, though occasionally the tone is decreased. This contrary effect is unexplained, unless 5HTP, like nicotine, stimulates both cholinergic and adrenergic postganglionic nerves The intestinal response to 5HTP is potentiated by an antihistaminic, inhibited by a benzyl analogue of serotonin and by anticholinergic drugs, and is unaltered by ganglionic blockage with hexamethonium (107). Anatomical and physiological studies indicate that 5HTP is produced and stored locally in the mucous membrane of the intestine, released in proportion to the rise in intraluminal pressure, and that it sensitizes pressure receptors Five-hydroxytryptamine probably has no primary function in the peristaltic reflex; however, it lowers the threshold of intraluminal pressure required to elicit the reflex and increases the frequency of contractions [Bülbring & Lin (108)].

Absorption and malabsorption—Studies of the digestive and absorptive processes in the normal human small intestine after a 500 gm fluid meal, containing fat in the form of corn oil, carbohydrate as glucose plus lactose, and protein as milk proteins, indicated that the meal is delivered from the stomach to the duodenum in small portions over a 4-hr. period (109). Absorption begins in the duodenum and is completed in the proximal 100 cm. of the jejunum, more proximal for fat than for carbohydrate and more proximal for carbohydrate than for protein.

The use of tagged neutral fat (I^{131} triolein) and fatty acid (I^{131} oleic acid) is helpful in the diagnosis of pancreatic insufficiency (110). I^{131} triolein requires pancreatic lipase for its hydrolysis prior to absorption; in the absence or deficiency of pancreatic lipase, the neutral fat is not absorbed appreciably, and is excreted in the feces. The oleic acid, on the other hand, does not require further lipolysis prior to absorption. A radioactive-tagged fat meal containing 48 per cent peanut oil, 48 per cent water, 4 per cent emulsifier, 20 gm. of barium sulfate, and 25 μc of I^{131}-labeled glycerol trioleate may be useful in studying digestion and absorption of fat (111). The amount of radioactivity in the blood reaches a plateau after 3 to 4 hr. and stabilizes for 6 hr. The fecal radioactivity for 48 hr. averages 0.6 per cent of the amount ingested, with a maximum of 1.4 per cent. Roentgen demonstration of a normal intestinal tract in patients with positive tests, low blood and high fecal radioactivity, indicates pancreatic disease. Radioactivity of whole blood is as efficient or more so than the radioactivity of plasma or its lipide fraction in the recognition of steatorrhea [Grossman & Jordan (112)] Measurements of the amount of radioactive vitamin B_{12} deposited in the liver 48 hr. after ingestion of $Co^{60}B_{12}$ may be another helpful diagnostic method (113). The absorption of B_{12} is impaired in patients with the primary malabsorption syndrome, and also in secondary malabsorption accompanying intestinal resection or blind loops; absorption is not improved by the administration of intrinsic factor (114).

Butterworth *et al.* (115) have studied patients with tropical sprue in relapse and find that they excrete less folic acid in the urine after oral than following parenteral administration, during remissions the absorption and excretion of folic acid are normal. The intestinal absorption of glycine after oral administration is delayed in untreated patients with sprue (116). Conversion of glycine to serine is not impaired, indicating that this pathway of glycine utilization is not impeded by the deficiency of folic acid. Patients with sprue also excrete significantly larger amounts of sucrose in the urine after oral ingestion than do normal persons, perhaps because of diminished hydrolysis of sucrose in the intestinal tract or increased permeability of the intestinal wall (117).

Butterworth has reported also that jejunal biopsies, obtained at operation 6 to 10 in. from the ligament of Treitz, disclosed in sprue, a thickening and blunting of the intestinal villi, decreased surface area, increased numbers of goblet cells, degeneration of columnar cells, and cellular infiltration with eosinophiles (118). The same type of mucosal atrophy also is observed in coeliac disease, suggesting an identity between the two disorders (119) This possibility is supported strongly by the study of suction biopsies performed by Rubin *et al* (120) in 65 patients, comprising idiopathic sprue, suitably aged controls, and active, latent, and adult coeliac disease; a specially designed flexible tube was utilized in infants and children, loss of villi, altered surface epithelium, chronic inflammatory infiltration, and crypt abnormalities were noted in both sprue and coeliac disease

Other types of steatorrhea.—Steatorrhea may accompany the syndrome of diverticulosis of the small intestine and macrocytic anemia. In one patient the impaired urinary excretion of vitamin B_{12} was unimproved by intrinsic factor but restored to normal by the administration of oxytetracycline. This and other observations suggested that vitamin B_{12} deficiency develops from bacterial interferences with intestinal absorption of this vitamin (121). Neomycin administered orally may produce a fecal excretory pattern resembling that of sprue; the abnormality disappears after withdrawal of the medication (122). Anderson & Langeford (123) recorded their findings on bacterial content of the small intestine in three conditions. In healthy children and in most patients with celiac or fibrocystic disease of the pancreas, they found the small intestine to be free of a resident fecal-type of flora, an observation not in accord with the hypothesis of bacterial competition with the host for essential nutrients.

Gluten in coeliac disease and sprue.—In patients with coeliac disease, digestion of gluten to the peptide stage appears to take place normally. Complete digestion of the peptide to the amino acid stage renders it harmless, whereas intermediate fractions remain active. After the administration of gluten, the blood glutamine rises to levels higher than normal, from which it may be inferred that the toxic effect of gluten is caused by the peptide-containing glutamine (124). There may be deficiency of a specific intestinal intracellular enzyme to deaminate the peptide-containing glutamine, or failure of the liver to remove glutamine peptides from the blood. Of 22 adult patients with idiopathic steatorrhea who were treated by French *et al.* (125) with a diet excluding wheat and rye glutens, 16 recovered completely; in 10 of these, absorption of fat later was demonstrated to be normal. The addition of gluten to the diet reprecipitated the symptoms. Thus, wheat gluten appears to be the basic cause of idiopathic steatorrhea in most, but not all, cases A favorable response in adults requires a longer period of time than in children, and a trial period of at least six months usually is desirable. Once normal health has been regained, the gluten-free diet must be continued indefinitely to avoid relapses.

COLON

Infections.—Gamble & Rowsan discuss the incidence of *Escherichia coli* in fecal specimens and state that certain types of *E. coli* may be pathogenic, producing gastroenteritis, especially among infants and children. Approximately one or two per cent of the adult population may be excreting pathogenic *E coli*, according to their conclusions (126) ECHO virus type 18 was isolated from the feces of premature and full-term infants in two separate but closely related outbreaks of epidemic diarrhea by Eichenwald *et al* (127) This probably is the first time a virus responsible for such an outbreak has been isolated by laboratory methods. Amebic infections of the colon may cause absence of haustrations and irregularities in the contour of the barium-filled colon, resembling the changes caused by ulcerative colitis (128).

Ulcerative colitis.—Kirsner & Elchlepp induced colitis in rabbits experimentally and found that the colon in rabbits responds to various immunological phenomena, including the Arthus and Shwartzman reactions A hemorrhagic "colitis" was produced in rabbits sensitized to egg albumin under conditions facilitating localization of antigen (egg albumin) and antibody in the colon, as in the Auer reaction (129). Repeated "Auer reactions" in the colon produced chronic inflammation and atrophy of the bowel wall The experimental findings, though not necessarily establishing an immunologic component in ulcerative colitis, stimulate interest in this possibility.

The daily intramuscular injection of methacholine bromide (Mecholyl) in oil produces bloody diarrhea in dogs. This response is more severe and sustained when Mecholyl is administered after erythrocyte and colon cholinesterases have been diminished by octamethyl pyrophosphoramide (130). The mucosal injury seems attributable to vascular damage caused by the intense muscular contractions of the colon. The possibility that ulcerative colitis may result from multiple etiologic agents is suggested by the clinical resemblance of lymphopathia venereum, acute vasculitis, scleroderma, and secondary amyloidosis of the colon to ulcerative colitis (131). The occurrence of ulcerative colitis and regional enteritis in multiple members of six families from the Bristol area of England again directs attention to possible hereditary influences in the pathogenesis of the two diseases, according to a study made by Houghton & Naish (132). The seromucoid levels in the blood are increased in patients suffering from ulcerative colitis and regional enteritis, while more accurate than the erythrocyte sedimentation rate or the C-reactive protein in assessing activity of intestinal lesions (133), the changes appear to be nonspecific.

Previous studies of rectal biopsy material had suggested that the initial lesion of ulcerative colitis is excessive destruction of the undifferentiated cells at the bases of the crypts of Lieberkuhn Similar findings were obtained by Lumb (134) in 130 colectomy specimens with only part of the bowel involved; it was assumed that the lesions at the junction of normal and abnormal mucosa represented the most recently acquired abnormalities. Carcinoma of the large bowel was demonstrated in 14 of 86 patients with ulcerative colitis who died from various causes, a ninefold increase in the frequency of death from colonic cancer in ulcerative colitis (135) The residual rectosigmoid stump after partial colectomy was the site of cancer in two patients.

The medical management of ulcerative colitis involves a comprehensive and sustained program of rest, sedation, antispasmodics, diet, restoration of nutrition, administration of electrolytes, blood, plasma, vitamins, iron, and antibacterial medication. Corticotropin and adrenal steroids continue to be useful therapeutic adjuncts Prolonged steroid medication may be desirable, though opinions differ (136, 137). Experience and increasing skill have reduced the hazards of corticoid therapy, permitting use of these drugs in more patients and for longer periods of time. In a comparative clinical and pathological study, perforation with fatal peritonitis developed in 10 of 400

patients treated before 1950, and in two of 250 patients treated with ACTH and adrenal steroids; there were no discernible significant differences in the histologic reactions in the two groups (138). The newer compounds, triamcinolone and 1,6-methylhydrocortisone, may be helpful in patients with diminished responses to earlier steroid preparations; however, their clinical effects are not spectacular. Rectal instillations of hydrocortisone and other steroids also may be effective (139). The blood levels of cortisol were unchanged following the rectal administration of 200 mg. of cortisol in 100 cc. of normal saline; similarly negative results were noted with cortisol-4-C^{14} (140). However, another study indicated that hydrocortisone was physiologically active in the body after its administration by rectal enemas and suppositories (141).

LIVER

Bilirubin.—The terms direct and indirect bilirubin have been replaced by the terms conjugated bilirubin and free bilirubin Direct-reacting bilirubin is a conjugation of lipide-soluble ("indirect") bilirubin with glucuronic acid. This combination probably occurs in the liver since, experimentally, liver tissue homogenates and slices containing liver microsomes will conjugate bilirubin in the presence of uridine diphosphate glucuronic acid, a glucuronyl donor in many glucuronide syntheses (142, 143, 144). Various chemical studies suggest that bilirubin is conjugated via its carboxyl rather than α-hydroxyl groups (145) and that the bilirubin-glucuronic acid complex is loosely linked to a mucoprotein (146) Bilirubin glucuronide is a mixture of two pigments (I and II) The more water soluble of these, pigment II, is predominant in human bile, both pigments I and II are found in the plasma and urine of patients with obstructive jaundice and with hepatitis; pigment I is in greater quantity, except in acute obstruction. Whereas both forms of conjugated bilirubin appear in the urine under such conditions, bilirubin does not. The chief bile pigment in the serum of adult patients with hemolytic diseases is free bilirubin, though small amounts of conjugated pigments I and II are present (142).

The absence of conjugated bilirubin in the plasma of patients with neonatal jaundice suggests a metabolic block in the excretory process (147). A similar situation has been noted in congenital hyperbilirubinemia, possibly because of a deficiency in the bilirubin glucuronyl transferase system. The glucuronyl transferase activity, as well as the uridine diphosphate glucuronic acid dehydrogenase activity are markedly deficient in the fetal and newborn guinea pig and gradually increase during the first few days of life. Since conjugation of bilirubin appears to be essential to its excretion in the bile, a defect in the glucuronide-forming mechanism would result in im-

has not been confirmed by other investigators (149). Congenitally jaundiced

Wistar rats have a defect in the microsomal enzyme system transferring glucuronic acid from uridine diphosphate glucuronic acid to bilirubin (150) No bilirubin glucuronide is demonstrable in the serum, bile, or urine; liver function tests are normal and the histologic appearance of the liver is normal. Bilirubin glucuronide, when injected intravenously, is excreted rapidly in the bile. These observations are interpreted to indicate that, despite a functioning excretory apparatus, excretion of bilirubin is severely impaired if glucuronide formation is defective. Similar observations have been made in patients with congenital nonhemolytic, nonobstructive jaundice.

A color reaction of bilirubin with the Lieberman-Burchard reagent was observed first in 1936 but not studied in detail then. This reaction, producing a bilirubin sulfate conjugate, is of interest because it yields an anionic complex of bilirubin with a prompt, direct diazo-reaction, suggesting that complexes of bilirubin with acid radicals other than glucuronic acid might be responsible for prompt, direct reactions (151). Serum bilirubin from infants with neonatal jaundice undergoes rapid photo-oxidation; free bilirubin is approximately three times as photosensitive as bilirubin glucuronide (152). Studies by Crosby (153) of severely injured patients given massive transfusions of whole blood and of healthy subjects given rapid infusions of distilled water to produce intravascular hemolysis, indicate a limit to the capacity for bilirubin production, regardless of the quantity of hemoglobin presented, the amount converted to bilirubin does not exceed two gm. per hour or approximately 50 gm. per day.

Enzymes, tissue reactants.—According to Bang *et al.* (154), the serum levels of various cellular reactants, including glutamic oxalacetic transaminase (SG-OT), increase in patients with parenchymal lesions of the liver, including hepatitis without clinically obvious jaundice. Serum glutamic pyruvic transaminase similarly aids the recognition and subsequent observation of nonicteric and icteric hepatitis complicating infectious mononucleosis (155). SG-OT decreased during cortisone therapy, in four of five patients with chronic active hepatitis, but not in five patients with chronic hepatic disease of different etiology (hemochromatosis, biliary obstruction), suggesting that cortisone reduces hepatic cell necrosis (156). The SG-OT may increase, at least transiently, in many illnesses including acute myocardial infarction, pericarditis, trauma of the chest and legs, uremia and pancreatitis, extremely high SG-OT values characterize multiple infarctions of the heart, lungs, or kidneys (157). A test based upon the release of 1-phosphofructaldolase into the serum, as a result of hepatocellular disease, is positive early in acute hepatitis and parallels the subsequent clinical course (158). The serum ornithine carbamyl transferase (OCT), one of the enzymes of the urea cycle, is elevated only in diseases of the liver (159). Isocitric dehydrogenase (ICD), a triphosphopyridine nucleotide-specific enzyme, is increased in actue viral hepatitis, averaging 15 times greater than normal. ICD, in contrast to other enzymes, was normal in all cases of extrahepatic obstructive jaundice (160). The serum cyanocobalamin (vitamin

B_{12}) level apparently is another sensitive index of hepatocellular damage; the values are increased early in acute viral hepatitis and are within the normal range in extrahepatic obstructive jaundice (161).

Mineral metabolism and immunological responses in hepatic disease.—In hepatolenticular degeneration, copper, in addition to its presence in the brain, is distributed throughout the hepatic cell cytoplasm; the amount of copper is not correlated with the presence or absence of symptoms; Kupffer cells are uniformly free of copper (162). Copper metabolism in cirrhosis of the liver was investigated by Gubler *et al.* (163) through measurements of total serum copper, ceruloplasmin, nonceruloplasmin copper, spinal fluid and urine copper, urine copper in patients given 2,3-dimercaptopropanol (BAL), and tissue copper in controls, and in patients with cirrhosis. Alterations in copper metabolism probably are not significant in the development of the neuropsychiatric manifestations of severe hepatic insufficiency. Altered zinc metabolism in patients with alcoholic cirrhosis is manifested by lowered concentrations of zinc in the serum, significantly depressed concentrations of zinc in the liver, and by increased urinary excretion of zinc. (164). The oral administration of zinc tends to reestablish normal urinary zinc excretion. Since both zinc and iron contents of the liver are disturbed, the metallo-enzymes of these metals presumably are the source of the biochemical defect.

Havens *et al.* (165) report that immunological hyper-reactivity may be demonstrable in patients with chronic hepatic disease with excessive production of tetanus antitoxin long after primary immunization was observed in patients with cirrhosis. Elevated titers of circulating complement-fixing antibodies to liver, kidney, and other human tissue antigens were noted by MacKay in a female patient with primary biliary cirrhosis (166).

Nutritional disorders.—Westwater & Fainer, investigating liver damage in the obese (167), report that obesity may be associated with fatty infiltration, focal inflammation, and fibrosis of the liver, together with abnormal hepatic function tests The abnormalities were found to subside with weight reduction Chronic malnutrition in adults produces similar changes in the liver, however, this factor alone without alcoholism, rarely suffices to produce cirrhosis (168, 169). Experimental studies involving various endocrine aberrations suggested that the rapidly developing fatty liver of malnourished African infants might be related to acute endocrine disturbances of the islets of Langerhans in the pancreas, the adrenal cortex, and the thyroid gland [Gillman & Gilbert (170)].

Three stages may characterize veno-occlusive disease of the liver, observed in the British West Indies and in India by Stuart & Bras (171): an acute phase, featured by sudden hepatomegaly and ascites, occurring usually in children one to six years of age; a subacute phase with persistent, often symptomless hepatomegaly; and a chronic stage, almost indistinguishable clinically from cirrhosis arising from other causes. The primary lesion is a widespread occlusion of the smaller and medium sized branches of the

hepatic veins, with a varying degree of sinusoidal congestion and necrosis of hepatic cells surrounding the central veins.

Chronic idiopathic jaundice.—Jaundice of the chronic idiopathic type is identified by the black appearance of fresh hepatic tissue and by the presence of coarse brown granules in otherwise normal-appearing hepatic cells (172). Males apparently are more susceptible than females. Jaundice recurs with fluctuating intensity and the clinical picture may suggest an obstructive process The pigment in serum behaves like bilirubinglucuronide; since the defective liver cells cannot excrete the conjugate into bile, as occurs normally, the pigment accumulates in the blood. The etiology of this inborn metabolic disorder is not known.

Cirrhosis.—In children under 15 years of age suffering from cirrhosis of the liver, the gross and histologic features resemble those of postnecrotic cirrhosis; hepatitis probably is the preceding event in approximately one-half of the cases (173) The cirrhosis was fatal within eight years after onset in 23 of 27 patients. In a series of 221 adult patients studied at autopsy by MacDonald & Mallory (174), who succumbed to postnecrotic cirrhosis, the age at death was the same as in patients dying of alcoholic cirrhosis. Carcinoma of the liver had developed in 14 per cent which was a high figure, esophageal varices were demonstrated in 52 per cent.

Chlorpromazine jaundice—The incidence of jaundice occurring during the administration of chlorpromazine approximates 1.0 per cent in hospitalized mental patients and 0 5 per cent in all other cases. Almost no jaundice occurs after five weeks' administration of the drug. While the icterus usually is brief, from two to four weeks, it may continue for months. (175). In 25 psychotic patients, studied by serial liver biopsies and function tests, the administration of 200 mg daily for three months produced histologic changes in five of 16 with normal biopsies prior to treatment and increased existing abnormalities in eight of nine patients (176). Studies conducted by Myers *et al.* with acetate-1-C^{14} in patients with chlorpromazine jaundice demonstrated greatly increased hepatic production of cholesterol and phospholipide (177)

Cirrhosis of liver—circulatory changes—The cardiac output may be increased in patients with portal cirrhosis of the liver (178, 179). The cause is not known, but may include lowered systemic resistance and arteriovenous fistula effects, with increased venous return Among 300 patients treated for portal cirrhosis, 131 of the deaths were attributable directly to the cirrhosis, including 67 with bleeding esophageal varices, 13 with primary carcinoma of the liver, and five with thrombosis of the portal vein and its branches (180). Whereas the great majority of deaths from bleeding esophageal varices occur during the first hemorrhage, 30 per cent of those with relatively little hepatic impairment may survive five years with medical management alone (181) The source of bleeding in 34 per cent of patients with cirrhosis who died of hemorrhage was not varices, but hemorrhagic gastritis, peptic ulcer and, to a lesser degree, lesions of the colon and the small intestine (182).

Percutaneous splenoportography with radio-opaque material Sodium acetrizoate (Sodium Urokon) is an excellent method of demonstrating lesions of the portal vascular system (183). Coeliac angiography, with a radio-opaque polyethylene catheter, demonstrates the coeliac artery and its branches and the vessels supplying the spleen, liver, pancreas, and stomach, without confusing visualization of the lumbar aorta [Ödman (184)]. A simple technique for measuring extrasplenic pulp pressure, presumably reflecting portal venous pressure and indicating a slight and temporary elevation during acute hepatitis, was devised by Reichman & Davis (185).

Experimental hepatic surgery.—Liver function may deteriorate in patients with cirrhosis of the liver treated by portacaval anastomosis, according to investigations reported on by McCredie *et al.* (186). In the search for surgical procedures improving hepatic function after portacaval operation, studies in dogs without cirrhosis indicated that arterialization combined with the shunt preserved function and general health better than the anastomosis alone. However, in dogs with carbon tetrachloride cirrhosis, portacaval anastamosis alone was tolerated better than portacaval shunt and arterialization. Hepatic artery flow alone is sufficient to maintain a relatively normal pH of the liver; portal vein blood flow alone is inadequate (187). End-to-side portacaval shunts, though reducing hepatic blood flow by approximately 50 per cent, do not alter significantly the volume of bile, cholic acid, bilirubin, or bile cholesterol in dogs (188). These moieties also are unchanged with arterialization of the portal circulation, increasing hepatic blood flow and elevating intrahepatic vascular pressure. Thus, biliary secretion seems independent of variations in portal blood flow and probably total hepatic blood flow, except in so far as the latter is necessary to maintain hepatocellular ingegrity

Vascular anastomoses—Injection of the portal vein at necropsy indicated prominent thoracic portacaval anastomoses in 10 patients with advanced cirrhosis of the liver (189). In two cases, injected material was present in the pulmonary vein and the left atrium. Similar venous pathways were demonstrated in patients with heart failure and without cirrhosis or cardiac disease, but they were less pronounced and did not involve the pulmonary veins These anastomoses conceivably may act as portapulmonary shunts, bypassing the lungs, and reducing the oxygen saturation of arterial blood.

Shunt operations for esophageal varices.—Direct end-to-side portacaval anastomosis is the most effective treatment for portal hypertension associated with esophagogastric varices and bleeding Portal pressure diminishes, varices may decrease in size, and the hazard of further bleeding is lessened. However, the long-term value of prophylactic shunts remains uncertain; and the state of the liver, not improved by the procedure, remains a critical factor determining the ultimate prognosis. The mortality of the operation is high and ideal criteria for surgery are rarely encountered. In a series of 47 patients, portacaval shunts were established in 29 with a mortality of 21

per cent; for 18 with splenorenal shunts, the mortality was 6 per cent, a collective mortality of 15 per cent (190); the incidence of bleeding decreased significantly after operation. Mortality during splenorenal anastomosis can be reduced by transfusions of fresh blood during the procedure and by hypotensive spinal anesthesia to reduce blood loss (191). Among 131 patients, 114 survived the procedure; esophageal bleeding recurred in only 16 of 92 patients observed for a year.

Redeker *et al.* have reported extensively on 10 patients with portacaval anastomosis Standard liver function tests and various data obtainable from catheterization of the hepatic vein were compared pre- and postoperatively. The estimated hepatic blood flow decreased, hepatic oxygen consumption did not change, wedged hepatic venous pressure uniformly decreased, and the hepatic vascular resistance was essentially unaltered. Hepatic function was not reduced significantly despite the substantial decrease in hepatic blood flow (192). Whereas the ingestion of glucose rarely increased hepatic vein wedged pressure (a reflection of sinusoidal and portal vein pressure) in normal subjects or patients with cirrhosis, the ingestion of meat increased the pressure in 7 of 12 cirrhotic patients; a less pronounced rise was noted in one normal person (193). Side-to-side portacaval shunts apparently may be helpful in the management of intractable ascites, based upon the concept that the primary difficulty is obstruction to the egress of blood from the liver and that the portal vein can act as a decompressive outflow route (194)

Portacaval anastomosis in dogs is accompanied by great loss of weight, anorexia, stupor, episodes of coma, and death (195). The coma closely resembles that following complete removal of the liver. In both instances, the quantity of free amino acids in the cerebrospinal fluid and the brain, predominantly glutamine, may increase appreciably While dietary manipulations and other therapeutic measures were unsuccessful in ameliorating this symptom complex, the prior establishment of a portal-systemic collateral circulation permitted such dogs to survive indefinitely without symptoms

Isolated homologous livers perfused with arterial blood by gravity flow are capable of producing bile and extracting a constant percentage of ammonia from the circulating blood (196). Normal dogs given ammonium chloride intravenously clear blood of excess ammonia more rapidly than fistula animals, with or without a donor liver Eck fistula dogs given ammonium chloride clear excess ammonia from the blood more quickly with a donor liver than without it. The infusion of various ammonium salts into the carotid circulation of dogs invariably produces coma, regardless of the subsequent change in blood pH (197). Characteristically, there is an early respiratory alkalosis followed by persistent acidosis The coma can be terminated by discontinuing the ammonia infusion, although the acidosis persists

Ammonia metabolism and hepatic coma.—Numerous conditions may precipitate hepatic coma in patients with liver disease, including excessive

drinking of alcohol, administration of ammonium compounds or diets high in protein content, infections, abdominal paracenteses, and gastrointestinal hemorrhage. Amino acid oxidase and urease, protein-splitting enzymes elaborated by coliform organisms, liberate ammonia which is subsequently absorbed and transported to the liver. Ammonia which is not utilized in the production of urea escapes to the systemic circulation either through the damaged liver or via collateral channels. The experimental intragastric administration of whole blood increases the level of ammonia in the blood in patients with cirrhosis or hepatitis, in contrast to healthy volunteers (198). The slow infusion of protein hydrolysates was well tolerated, but rapid administration produced impending coma with pronounced increases in venous blood ammonium concentration (199). The presence of glutamine or aspartic acid or both in the hydrolysate solution could prevent a prompt increase in the blood ammonia. The practical implication of these observations is the removal of ammonium from or the addition of ammonium-neutralizing or detoxifying substances to protein hydrolysates for use in patients with severe liver disease. Increases in blood ammonia after the ingestion of methionine were not observed when the same cirrhotic patients were pretreated with neomycin sulfate orally (200). Previous investigations have demonstrated in patients with hepatic insufficiency, systems in the extremities and the brain capable of removing ammonium from the circulating blood. Poor ammonium removal was demonstrated in some patients with cirrhosis or coma and in cirrhotic patients with blood in the gastrointestinal tract (201).

Individual plasma amino acids, measured by column chromatography in patients with liver disease, rose with the increasing severity of the process, but were not always elevated in hepatic coma (202). Methionine and tyrosine, as had been noted previously, were elevated disproportionately. Sodium glutamate given intravenously was metabolized rapidly and normally in patients with severe hepatic insufficiency. A diagnostic test for impending hepatic coma was based on changes in the electroencephalogram after the administration of a high protein diet, ammonium salts, urea, or methionine; the mechanism may be decreased cerebral utilization of oxygen (203).

Treatment of elevated blood ammonia.—The treatment of ammonia intoxication is designed to reduce the blood ammonia and the quantity of ammonia entering the portal circulation (204, 205, 206). In patients with severe hepatic disease, the production of ammonia within the gastrointestinal tract may be limited by decreasing the intake of protein, control of bleeding, prompt removal of blood in the digestive tract by lavage or catharsis, and by the oral administration of antibiotics to decrease ammonia-producing bacterial activity Arginine is considered the most effective of the urea cycle intermediates because of its free permeability into the hepatic cells and the high concentration of arginase in the liver, permitting arginine to act as a precursor to ornithine (204). The *in vitro* rate of urea formation from ammonia by liver cells was accelerated by the addition of arginine or ornithine

to the reaction. The rise in urea nitrogen in protected rats suggested that the major effect of arginine was mobilization of the Krebs-Henseleit urea-synthesizing cycle (207). Similarly, rising urea nitrogen was noted in glycine-poisoned dogs and in humans with hepatic coma treated with arginine. The administration of arginine hydrochloride, 500 ml. of a 2 per cent solution in 10 per cent dextrose, effectively controlled ammonia intoxication in 48 of 50 patients; the mechanism of action is the accelerated amidation of glutamic or aspartic acid and the formation of urea (204). Despite these favorable theoretical and experimental considerations, L-arginine administered intravenously did not lower blood ammonia or induce consistent clinical improvement in patients with advanced liver disease and hepatic encephalopathy (208). L-arginine, similarly, was ineffective in subjects with normal hepatic function in whom the blood ammonia was elevated by the intravenous administration of ammonium salts. On the other hand, L-arginine reduced the rise in blood ammonia resulting from the intravenous infusion of glycine or from the administration of an arginine-deficient L-amino acid, to fasted subjects The findings indicate that L-arginine prevents or reduces elevated blood ammonia levels when it acts at the site of ammonia release; however, it appears to be of limited value in reducing elevated blood ammonia levels when the source of the ammonia is primarily exogenous, as in most instances of hepatic encephalopathy (209). Neomycin given orally, in contrast to glutamic, aspartic or lipoic acid, cortisone and hydrocortisone, was helpful to patients in acute hepatic coma, and to those with chronic hepatic encephalopathy (208). Fetor hepaticus was abolished in six of seven patients The effect of neomycin on the identifiable fecal flora varied and was not correlated with the clinical effect or the fall in blood ammonia Despite the problems associated with excessive nitrogenous material in the digestive tract of patients with severe hepatic disease, an adequate protein intake and abundant calories are essential in correcting the protein depletion in cirrhotic patients The fear of protein toxicity should not discourage a nutritious diet in the patient who requires and tolerates it (210). Other abnormalities in patients with hepatic insufficiency include potassium and magnesium deficiency, lack of essential metabolites such as serotonin precursor, coproporphyrin retention, and alterations in carbohydrate metabolism (205).

Adrenal steroids and bile metabolism—The jaundice of hepatitis often diminishes rapidly during the administration of ACTH, as though corticotropin possessed choleretic and hydrocholeretic properties. However, studies of the plasma clearance of sulfobromophthalein, the percentage disappearance rate of I^{131}-labeled rose bengal from the plasma, the volume, concentration, and total output of bilirubin after cortisone and hydrocortisone taken orally and hydrocortisone intravenously, failed to demonstrate a choleretic action for these compounds (211). Hydrocortisone and cortisone did not increase the secretion of bile in cholecystectomized dogs (212). Negative results also were observed in ten postcholecystectomy patients, with a T-tube

in the common bile duct, given 100 mg. of hydrocortisone intravenously (213). Cortisone and prednisone also reduce the hyperbilirubinemia in complete biliary obstruction, though to a lesser degree than in acute hepatitis (214); conjugated bilirubin in the urine decreases concomitantly, suggesting that steroids may act directly on the liver. The therapeutic value of adrenal steroids in hepatic disease remains uncertain. Very large doses of steroids abolished the coma in patients with advanced cirrhosis and severe hepatic insufficiency, but the coma relapsed and all patients died of complications of the disease (215, 216). The mechanism of the response is obscure; perhaps steroids temporarily stimulate brain metabolism.

Ascites in cirrhosis of liver.—The retention of water and the hyponatremia in portal cirrhosis remains unexplained but do not appear related to persistent or excessive amounts of antidiuretic hormone; indeed, the cirrhotic liver can dispose of the antidiuretic hormone and other hormones of the anterior pituitary normally. Additional studies emphasize the excessive reabsorption of sodium and water from the proximal tubules. Delivery of a sufficient volume of glomerular filtrate from proximal to distal sites with "osmotic" diuretics (e g , mannitol) produces more free water in cirrhotics than in normal subjects (217). The administration of chlorothiazide (Diuril) may produce an effective diuresis in patients with cirrhosis of the liver and ascites (218). The excretion of potassium in the urine increases, necessitating supplementary potassium medication. As with acetazolamide (Diamox), impending or actual hepatic coma developed in 7 of 13 patients treated with chlorothiazide, usually accompanied by elevations in the fasting arterial ammonia level.

The possibility that the excessive salt and water retention in a patient with postnecrotic cirrhosis and massive refractory ascites might be related to excessive production of aldosterone led to a bilateral adrenalectomy (219). Grossly and histologically, there was no adrenal hyperplasia. The urinary sodium increased greatly and aldosterone disappeared from the urine. The progressive loss of ascites appeared to be attributable to the surgically-induced hypoaldosteronism. Amphenone B, related structurally to the synthetic estrogens, inhibits both thyroid and adrenocortical activity in animals and man, decreasing production of aldosterone; this effect may or may not be accompanied by increased urinary excretion of sodium or by clinical improvement (220, 221). In three patients with cirrhosis and ascites, amphenone B, in doses up to 6 gm. daily for three to seven days, preceded and followed by courses of prednisone, produced sodium diuresis with weight loss, presumably as a result of suppressed production of aldosterone (220). In another study, amphenone B, in doses totalling 11 to 18 gm. in three to four days, induced sodium-diuresis in two of four patients; transient impending hepatic coma developed in both instances (221) The associated adverse neurological effects and the general toxic effects of amphenone B limits its clinical application.

GALLBLADDER

Tolerance for fat.—The ingestion of butter, margarine, and olive oil to 100 gm. is well tolerated by patients with various types of hepatic disease (222). Absorption of these fats is not decreased in patients with uncomplicated cholelithiasis or in those recovering from hepatitis Malabsorption of fat was noted in patients with biliary obstruction, biliary fistula, cirrhosis with jaundice, or with active hepatitis in the obstructive phase. Even in the presence of total obstruction of the biliary tract, approximately 50 per cent of the fat ingested was absorbed The studies thus indicate that patients with hepatic disease or with uncomplicated gallbladder disease may be given considerable quantities of butter, margarine, or olive oil.

Gallstones.—The observation of partial obstruction of the biliary tract at the ampulla, at the time of cholecystectomy for cholelithiasis, led to studies on the role of narrowing of the ampulla in the production of gallstones (223). In dogs, rabbits, and monkeys, experimentally produced biliary stenosis resulted in the formation of stones in the gall bladder and the bile duct, even when the bile remained free of bacteria. Electrophoretic studies indicate that the gallbladder mucosa secretes a lipoprotein holding pigment and cholesterol in solution, while bile is being concentrated, disease of the gallbladder decreases the lipoprotein, thereby reducing the stability of bile and favoring the formation of gallstones. Abnormal proteins resembling albumin and mucin also appear in the bile and may play a role (224). The low cholesterol concentration in dog bile is an important factor in the solubility of gallstones; phospholipides and bile acids also may increase the solubility of gallstones (225)

PANCREAS

Experimental pancreatitis.—Pancreatitis may be produced experimentally by obstruction of the ducts, impairment of the blood supply of the pancreas, mechanical or chemical trauma, metabolic disturbances, and by local anaphylaxis. Obstruction of the flow of pancreatic juice, when accompanied by mild interference with the arterial supply or venous drainage of the pancreas produces acute hemorrhagic pancreatitis. The presence of thrombi in the arterioles and venules of the pancreas suggests a contributory role of vascular thrombosis, pancreatitis did not develop under the same experimental conditions when thrombosis was prevented by anticoagulation (226). Propylthiouracil appeared to retard the progress of experimental pancreatitis, perhaps by decreasing the metabolic activity of the pancreas (227). Species differences in the anatomy of the pancreatic ductal system and its relationship to the common bile duct and the unusual experimental conditions limit the clinical application of animal studies, mechanical factors appear to be especially significant in the human disease, although vascular and metabolic disturbances may prove to be important (228). Atheromatous embolization from the aorta to the pancreatic arteries in 12

autopsy cases, 10 with an associated acute pancreatitis, appeared to indicate a vascular component in acute pancreatitis according to findings reported by Probstein *et al.* (229).

Measurements of pancreatic and biliary intraductal pressures in dogs without disturbing the sphincteric mechanism yielded interesting observations (230). In intact dogs, pancreatic intraductal pressure invariably exceeds the pressure at the common bile duct. After cholecystecomy, biliary pressure occasionally exceeds pancreatic pressure. In obstruction of the pancreatic duct, the pancreatic secretory pressure initially exceeds the secretory pressure of the liver and then decreases. Variations in secretory pressure of the obstructed pancreas may explain the variable increases in pancreatic intraductal pressure after the injection of morphine. After morphine, the pancreatic intraductal pressure and plasma amylase increase, probably as a result of the sphincteric action of the duodenal mucosa surrounding the intraductal segment of the ducts Pancreatic intraductal pressure rises after the intraduodenal introduction of alcohol, perhaps explaining the frequency of acute pancreatitis after a large intake of alcohol.

Clinical pancreatitis.—The study of 179 fatal cases of acute pancreatitis made by Bell (231) indicated gallstones as the principal cause in about one-third of the men and one-half of the women after the age of 40 In persons under 40 years of age, alcoholism was more important than cholelithiasis. In four alcoholic patients with clinical diagnoses of acute pancreatitis studied by Albrink *et al* (232) attacks of abdominal pain following alcoholic debauches were accompanied by pronounced, transient lactescence of the serum; there was evidence of hyperlipemia, especially of the triglyceride fatty acids, probably secondary to the pancreatitis. Cope *et al.* (233) suggest that pancreatitis may be another complication of hyperparathyroidism as a consequence of the formation of pancreatic calculi and ductal obstruction; *in one patient, the pancreatitis was found to subside after re*moval of the parathyroid adenoma. Chronic relapsing pancreatitis occurring in families suggested to Gross & Comfort that the hereditary disease may be transmitted as an autosomal dominant gene (234). Familial pancreatitis resembles the sporadic disease in most respects. However, it begins earlier in life, affects females predominantly and, thus far, is unassociated with alcoholism or gallstones Alpha-benzoyl-l-arginine amide hydrochloride is hydrolyzed rapidly by trypsin to yield benzoyl-l-arginine and ammonia; the quantity of ammonia released is considered proportional to the quantity of trypsin in serum. In a small series of cases reported by Nardi & Lees (235), the serum trypsin appeared to be a more sensitive and reliable index of pan[illegible]

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[illegible] ock and de-creases the mortality in acute pancreatitis; room-stored plasma may be utilized similarly (236) Kaplan reported that cortisone appears to be effective in the treatment of severe acute pancreatitis although the mechanism

of action is not known (237). Corticotropin (40 mg.), hydrocortisone (100 mg), or prednisolone (50 mg) given intravenously, significantly lowered the rate of flow of external pancreatic secretion and the rates of bicarbonate and amylase production in patients with and without inflammatory disease of the pancreas. However, decreases were not so pronounced as to justify the use of these compounds in the treatment of pancreatitis; the diminished secretion may be related to damage to the pancreatic acinar tissue (238).

An effective method for relieving the pain of chronic pancreatitis apparently is to interrupt the sensory pathway and reflex arc to and from the pancreas, by sectioning the postganglionic fibers just before the pancreatic substance is reached (239). Most of the postganglionic fibers from both celiac ganglia join, forming a large bundle (the "plexus pancreaticus capitalis"), accessible to section, the bundle enters the medial margin of the uncinate process of the pancreas Carbohydrate metabolism and external secretion are not disturbed after section of the plexus Pain was relieved completely in 35 of 36 patients with chronic pancreatitis, with no recurrence for periods up to five years postoperatively.

Glucagon.—Glucagon, secreted by the alpha cells of the pancreas, seems to participate in the regulation of blood sugar It has been demonstrated in the blood of patients with refractory peptic ulcer associated with noninsulin producing islet cell tumors of the pancreas. The effect of glucagon upon external pancreatic secretion was studied because of the possibility that a decrease in the alkaline pancreatic secretion might contribute to the development of the peptic ulcerations (240) Moderate and large doses of glucagon administered intravenously increased pancreatic secretion transiently, then reduced the secretion for periods up to two hours Dreiling *et al.* found in human studies, that glucagon 2.0 mg given intravenously did not alter external pancreatic secretion, either in patients with and without pancreatic disease (241).

Exfoliative cytology.—A rapid, easily performed method of duodenal intubation devised by Raskin *et al* (242) facilitates duodenal drainage in patients suspected of carcinoma of the pancreas or biliary tract. Exfoliative cytologic study of this area is improved further by the use of secretin intravenously to stimulate pancreatic secretion Malignant cells were recovered in 28 of 43 cases of carcinoma of the pancreas, biliary tract, gall bladder, and duodenum, utilizing these techniques

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DISEASES OF THE CARDIOVASCULAR SYSTEM[1] (EXCLUDING HYPERTENSION AND ATHEROSCLEROSIS)

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ELECTROCARDIOGRAPHY

Electrocardiography has continued to be an active field, with studies relating to intraventricular conduction and leads or lead systems suitable for vectorcardiography contributing heavily. The important and controversial problem is still undecided regarding the nature of excitation of the free wall of the left ventricle, namely, whether the subendocardial muscle is activated in a rapid and chaotic fashion with only the epicardial layers contributing substantially to the QRS complex as recorded in external (direct or semidirect) leads, or whether radial spread of excitation occurs through the entire wall of this chamber. The group of workers (1) whose studies have favored the latter view have provided no further evidence to support it, but in investigations using the same techniques, have shown that in the dog with left branch block the septum is excited from right to left, with the left ventricle activated earliest on the anterior, epicardial aspect. The latter causes excitation to pass inward toward the cavity of the left ventricle for a short time. In experimental studies and limited observations on the human heart directed toward an analysis of the form of the QRS complex in epicardial leads, Pipberger and his associates (2) have confirmed their earlier impression that only the outer layers of the left ventricle contribute significantly to the R wave seen in epicardial leads. The implications of these observations, particularly in myocardial infarction, were pointed out and in this connection, the frequent occurrence of a QRS complex with a small initial r wave and large S wave (rS) in the epicardial lead over an infarct was mentioned.

Sodi-Pallares and his colleagues (3), in ingenious experimental studies, attempted to relate pathways of ventricular activation to findings in vectorcardiograms This was done by determining the locations of maximal positivity and negativity on the epicardial surface of the ventricles at a number of instants of time during excitation These they designated as the "apparent maximal potential gradients" and, when represented by vectors, made it possible to construct vectorcardiograms in the three usual planes. These vectorcardiograms were compared with vector figures recorded by the use of the cube system of electrode placement, and agreement was sufficiently close to justify the conclusion that vectorcardiograms give "valuable in-

[1] The survey of the literature pertaining to this review was completed in August, 1958

formation on the sequence of ventricular activation." The reviewer wonders if the use of a better electrode system, rather than the cube arrangement, might not have made the results even more impressive.

Much work has been done relating to the electrocardiogram in bundle branch block or other types of abnormal intraventricular conduction, and studies by Chapman & Pearce (4) are probably of the most clinical importance. These investigators studied a large number of electrocardiograms showing left bundle branch block taken on patients with myocardial infarction known to be present either from autopsy findings or from electrocardiograms taken at suitable periods when intraventricular conduction was normal. On the basis of this study, it was suggested that the common impression that the electrocardiogram loses much or all of its diagnostic value when left branch block exists, is not correct. Specifically, Q waves in leads I, aV_L, and V6, and failure of R waves to increase in size in precordial leads taken in the usual fashion, were found with extensive anteroseptal infarction and, with less marked involvement of the same region, rsR′ complexes in these leads and deep notching of the S (or QS) wave in the precordial tracing taken just to the right of the transitional zone were present. With posterior infarction, notching of the R (or R′) wave in a V_F was seen. Some of these alterations in the QRS complexes, especially those occurring with posterior and septal infarcts, are minor in character and should be used with caution until more evidence is available which points to their reliability. Nevertheless, the work of Chapman and Pearce is of great interest and may prove to be of considerable clinical importance.

Angle (5) has devised a method for recognizing myocardial infarction in the presence of anomalous A-V excitation (Wolff-Parkinson-White syndrome). The method requires both a pre- and postinfarction tracing and involves an ingenious but rather complicated vector analysis of the records Pick & Fish (6) have described the simultaneous occurrence of bundle branch block and W-P-W syndrome in three patients and point out that this may be recognized only when pre-excitation occurs in the ventricle with the intact bundle Studies on eighty patients with W-P-W syndrome (7) indicated that 60 per cent had no evidence of organic heart disease and 56 per cent had arrhythmias. Two older patients in this group died, presumably from a serious arrhythmia, but the prognosis in those not subject to attacks of rapid heart action was excellent. Observations of a patient with this pre-excitation syndrome (8) revealed several different types of arrhythmia and were believed to support the idea that an accessory pathway between atria and ventricles is the cause for the anomalous conduction. It has been known for many years that this type of conduction may be transient and sometimes may alternate with normal intraventricular conduction for no obvious

larly. In two patients he studied, normal intraventricular conduction appeared with deep inspiration in one and with expiration in the other.

Patients with intermittent bundle branch block often develop the conduction defect with an increase in the heart rate and then have normal intraventricular conduction return when the rate decreases. In such a patient with left branch block, Gardberg & Rosen (10) discovered that the rate at which the block would appear during acceleration was higher than that at which normal conduction would return in the period of slowing immediately thereafter. They offer a logical and ingenious explanation for this phenomenon.

The term "masquerading" bundle branch block has been used to describe a type of intraventricular block in which the limb leads suggest left and the precordial leads right branch block. On the basis of electrocardiographic and pathologic studies, Unger and his associates (11) suggest that these somewhat unusual tracings may be caused by incomplete bilateral bundle branch block and advise that the term "masquerading" be dropped. The reviewer would give similar advice, since most such tracings are probably examples of complete right branch block with a vertical or semivertical heart which causes the limb leads to resemble left branch block.

Vectorcardiographic studies on patients with left branch block, done with the Frank 7-electrode system, by Frimpter and associates (12) indicate the usual existence of an initial QRS vector directed anteriorly and commonly to the left. This vector was also occasionally oriented to the right, causing Q waves in lead I, aV_L, and precordial leads from the left side. The latter observations are particularly interesting since the patients with these Q waves did not have histories suggesting previous myocardial infarction, and cast some doubt on the observations of Chapman and Pearce, mentioned above. It must be remembered, however, that the Frank scheme for orthogonal leads, although superior to many in common use, is not the best now available and might be particularly inaccurate in patients with bundle branch block.

There appears to be a growing realization on the part of many vectorcardiographers that the leads generally employed for recording such records with the cathode ray oscillograph are poor ones, since they do not provide transverse, vertical, and sagittal components of cardiac voltages in even approximately pure form. It is further becoming clear that better leads or lead systems for vectorcardiography which are practical for routine clinical use are now available and that good orthogonal leads of this kind may be satisfactory for ordinary scalar electrocardiograms as well as for vector records. Abildskov and his associates (13) have studied scalar records taken with Frank's system and believe that the three tracings so obtained depict most but not all of the abnormalities observed in the conventional 12 lead electrocardiogram. Pipberger (14) has made observations with the 14 electrode orthogonal lead system of Schmitt & Simonson (15) on 100 normal

subjects, using scalar as well as vector records. He found that although the range for the direction of the maximal QRS vectors in the frontal plane was considerably smaller with the lead system mentioned than when conventional leads were employed, other parameters were not significantly different. Simonson and his colleagues (16) compared a number of orthogonal lead systems and conventional leads in a group of normal subjects, using changes in the mean QRS and T vectors with respiration as indices of lead behavior. It was concluded that electrocardiographic changes occurring with respiration can not be explained by alterations in the position of the heart alone, and the greatly different results obtained with different lead systems point to the need for general agreement in the arrangement to be used. The first conclusion mentioned above is supported by studies done by Lamb (17) on the effects of respiration on the conventional electrocardiogram. This worker presents evidence which indicates that respiratory changes in such tracings are related to expected alterations in the stroke volume of the right and left ventricle In contrast to this point of view, examples of alternation in the size and form of electrocardiographic complexes observed in patients with pericardial effusions are reported by Littmann & Spodick (18). In these cases, the changes were felt to be due to movements of the heart, especially about the long axis.

Langner *et al.* (19) have compared four of the recently developed and probably best systems for obtaining orthogonal leads by registration of vectorcardiograms in 60 subjects with both normal and abnormal hearts and conclude that the different arrangements give similar results in most instances. In five patients evidence was found to show that the leads for the sagittal (z) component gave significantly different voltages, and in 3 patients the vertical (y) components were somewhat dissimilar.

Burch and his associates (20), in a study of the spatial vectorcardiogram using the equilateral tetrahedral reference system, conclude that distortion of the QRS loops is seen with increasing frequency in aging. Dower & Osborne (21) propose a relatively simple 4-electrode system for vectorcardiography which they believe compares favorably with Frank's 7-electrode arrangement. Burger & Vaane (22), in a study of the orientation of the vectorcardiogram in space, use a new quantity, the polar vector, as an index. The length of this vector is proportional to the area of the QRS loop, and its direction is perpendicular to the plane in which the loop lies. Using transparent spheres, the authors show that the orientations of the polar vectors [illegible] with patients having right [illegible] block.

[illegible] studies on patients with coronary artery disease and intraventricular conduction defects, using [illegible]

[illegible] such poor representations of the transverse, vertical, and sagittal components

of cardiac voltages that one cannot rely on the accuracy of vectorcardiograms obtained by means of this technique.

Vectorcardiographic studies, again using the cube system, were done on patients and dogs with hypothermia (24), and on patients with interatrial septal defects (25). Many interesting problems are discussed in these papers but, for reasons mentioned above, the reviewer does not take the vectorcardiographic data very seriously. Fischmann (26) has used the leads of the cube system to record ordinary scalar electrocardiograms and believes that left ventricular hypertrophy may be recognized from the three tracings so obtained.

The above discussion emphasizes the need for the standardization of technique for registration of vectorcardiograms, especially in connection with the leads to be employed. This matter cannot be settled until there is more understanding of the nature of the problem and more agreement relative to its best solution than that which exists today. The reviewer may, of course, be prejudiced but believes that the lead field concept proposed several years ago by McFee & Johnston (27) points to the best and simplest techniques for obtaining good orthogonal leads which may be used for either vectorcardiograms or scalar tracings Except for a few workers like Brody and Helm, there has been little indication that the lead field idea has been understood or appreciated by cardiologists in this country.

Interesting studies of the effects of multiple dipoles immersed in tap water were reported by Okada (28). In a homogeneous conducting medium two separated dipoles caused boundary potentials which could not be simulated by a single dipole, but a symmetrical array of four or more could be closely represented by a single dipole. In further studies, designed to represent the increased conductivity of blood within the heart, it was found that boundary potentials were modified so that two separated dipoles behaved much more like a single equivalent source than was true with a homogeneous medium The latter studies emphasize the importance of earlier work of Brody and his co-workers (29) Brody (30) recently developed an immersion technique for obtaining unusually accurate vectorcardiograms in the frog. The method eliminates most of the variables and uncertainties inherent in other lead arrangements. It is not independent of nonhomogeneity in resistance of the body of the frog, but it is likely that the higher conductivity of blood within the cavities of the heart is the only important disturbing factor here.

Several investigators have studied the electrocardiographic findings in ventricular hypertrophy In relation to right ventricular hypertrophy with [illegible] t if the [illegible] +110° [illegible] the R or R′ wave is more than 0.5 mv., the tracing points to right ventricular hypertrophy Vectorcardiographic studies, employing a cube system, were also done in connection with this work. Wasserburger & Brown (32), in

extensive studies in both children and adults, emphasize the value of a prominent late R wave in aV_R as an index of right ventricular hypertrophy in all age groups. They believe that incomplete right branch block and right ventricular hypertrophy often coexist, especially in patients with congenital heart disease, and think that the typical electrocardiographic findings under these circumstances are a late, prominent R wave in aV_R, an R′ wave of 10 mm. (1 mv.) or more in V_1 or V_{3R} with delay of the R′ of varying degree depending on the age of the patient, and qrS complexes in the left precordial leads. On the basis of correlations between data obtained by intracardiac catheterization and electrocardiograms they do not believe that the relationships between systolic and diastolic overloading of the ventricle and electrocardiographic findings proposed earlier by Cabrera & Monroy (33) are entirely valid. Studies by Hoffman (34) suggest that in infants and children ranging in age from one month to fifteen years an R/S or R/Q ratio of over 1.0 in aV_R and an R/S ratio in V_1 of from 7.0 to 1.5, depending on the age group, are the most reliable criteria for right ventricular hypertrophy. In the patients younger than one month the R/S or R/Q ratio in aV_R is not a reliable guide, but in this group an R/S ratio in V_6 of 0.6 or less is suggestive of right ventricular hypertrophy. The criteria for right ventricular hypertrophy were evaluated on the basis of pathologic findings.

A study of 101 patients whose electrocardiograms showed no abnormality except large QRS complexes, using criteria previously established, were shown by Grubschmidt & Sokolow (35) to have clinical evidence pointing to cardiovascular disease in 95 instances. In most of these, left ventricular hypertrophy was believed to be present. Furthermore, large voltage of the QRS complexes was felt to be an early sign of such hypertrophy. Selzer and his associates (36) studied 108 tracings which fulfilled the commonly accepted criteria for left ventricular hypertrophy but found clear pathologic evidence of such hypertrophy in only 75 of these patients. Of the several electrocardiographic criteria for hypertrophy of the left ventricle, increased voltage of the QRS complexes in the chest leads was the most sensitive index, but this was also responsible for a false positive diagnosis most frequently. The authors conclude that the electrocardiographic diagnosis of left ventricular hypertrophy is only moderately satisfactory and is particularly disappointing in early hypertrophy of this chamber

In a study of 85 patients with QRS complexes of the rS type in chest lead V_6 and autopsy evidence available, Goodwin (37) found that although a number of the hearts showed simple right ventricular hypertrophy, myocardial infarction, most frequently anteroseptal in location, or combined (right and left) ventricular hypertrophy or both, were also common findings. The close resemblance between the electrocardiograms seen in right ventricular hypertrophy and anterior infarction was emphasized

Richman and his co-workers (38) made careful pathologic studies, with the Schlesinger technique, on the hearts of 55 patients who had shown QS deflections in right precordial leads (V_1–V_3 or V_{3R}). The electrocardiograms

were classified in four groups, depending on the initial deflections in V_E and V_6. It was concluded that in the absence of left branch block QS deflections in the right precordial leads were diagnostic of anterior infarction, often in the region overlying the septum, and when QS waves were present in V_E significant involvement of the septum as well was usually present. In one of the groups, where left branch block was present, it was found that the conduction defect interfered with the diagnosis of infarction. Chapman & Pearce (4), as mentioned earlier, might not agree with the latter conclusion.

Cutts *et al.* (39) have studied 69 patients who had chest pain of the "coronary" type and whose electrocardiograms were normal except for deeply inverted T waves especially in the chest leads. In a follow-up period of about four years almost half of the group were leading a reasonably active life, but in 24 who had died, more than half of the deaths were known to result from heart disease. Seven of these patients died within the first year of observation and all of the 11 autopsied patients were found to have extensive atheromatous changes in and narrowing of the coronary arteries. Only a few small healed infarcts were found. The reviewer feels, as do the authors, that in patients whose histories point to true heart pain, T wave changes of the kind described are usually caused by myocardial ischemia related to more or less extensive coronary artery disease, but thinks the importance of the history in evaluating the significance of such T waves cannot be overemphasized.

Pappas (40) found 14 patients in a group of 742 with myocardial infarction in whom QRS changes present in the early electrocardiograms disappeared entirely in subsequent tracings. The cause for this unusual finding was thought to arise from shrinkage of the infarct, with healing, so it was no longer detectable in surface leads Development of collateral circulation which restored normal excitation to muscle where it was initially absent, was also suggested as a possible explanation.

August and his colleagues (41) describe marked changes in the form of the ventricular complexes in chest leads, on deep breathing, in three patients with coronary artery disease. Great variation in the size and form of the QRS complexes was observed, with some showing much more marked changes pointing to infarction than did others, while less marked alteration was seen in the T waves. Although the striking changes in the QRS complexes noted here are interesting the reviewer does not agree with the implication that electrocardiographic changes simulating infarction are likely to occur as the result of respiratory changes or slight shifts in the position of chest electrodes.

Manning (42) discusses exercise tests for coronary artery disease in a sane and sensible fashion His suggestions that the amount of exertion should not be standardized but should depend on the patient under investigation and that no arbitrary criteria for a positive test should be followed, are in harmony with the opinion of the reviewer The importance of even slight depression of the RS-T segment in the postexercise tracings may be

great, if it is of the "flat" type rather than having an upward slope. The writer further believes that an accurate, complete history will decide the nature of chest pain in most patients and exercise tests are rarely necessary, except in special groups, such as individuals applying for insurance, where the history may be incomplete or even inaccurate. When such tests are done, they should be carried out by a physician familiar with the patient and not by a technician.

Many of the articles referred to above are concerned, in one way or another, with congenital heart disease but an excellent paper by Sodi-Pallares *et al* (43) summarizes much of the current knowledge about the electrocardiogram in patients with congenital cardiovascular defects, and outlines an approach which should increase the diagnostic value of the tracings considerably. The authors point out that congenital lesions of different kinds (both in the cyanotic and acyanotic groups) are associated with mean manifest electrical axes of QRS (ÂQRS) which are oriented in quite characteristic directions and if, in addition to this, other peculiarities of the tracings commonly seen with certain defects are noted, the electrocardiogram alone may reveal the basic anomaly which is present.

Wasserburger *et al.* (44) suggest that, in patients with pulmonary emphysema with tall, peaked P waves in lead II, the atrial recovery wave, T-a, causes exaggerated depression of the segment between the end of P and the beginning of QRS and the succeeding R-ST segment as well. The proposal is an interesting one but the critical reader might wonder if the depression mentioned, especially of the R-ST segment, is not caused by digitalis.

Macruz and his co-workers (45) describe a simple and logical method of differentiating between right and left atrial enlargement by determining the ratio between the duration of the P wave and that of the P-R segment. This ratio in normal subjects (or patients without atrial enlargement) varies between 1.0 and 1.6. With right atrial enlargement the ratio is less than 1.0, and with left atrial enlargement over 1.6, as a rule.

Barbato *et al* (46) have made detailed observations with leads taken directly from the epicardial surface of the heart at the time of surgical procedures for pulmonary disease, in a number of patients with normal hearts. Among other things, it was found that QRS complexes of the rS type were predominant on the anterior surface of the right ventricle, and Q waves were constantly found in the tracings obtained from the anterolateral surface of the left ventricle. In one patient demonstrating small QRS complexes in lead I and S waves in all standard leads the epicardial leads were quite different from the others, supporting the idea that excitation is unusual in

(*a*) Appearance of S waves in lead I and Q waves and inverted T waves in

III with inverted T waves in chest leads over the right ventricle. (*b*) S waves in lead I and inverted T waves in III or appearance of inverted T's in III with inverted T waves in chest leads over the right ventricle. (*c*) Appearance of S waves in I and Q waves and inverted T waves in III with right bundle branch block.

Davies (48) has written an interesting report indicating the inconsistency of electrocardiographic interpretations even among experienced observers. Nine individuals, considerably experienced in the use of electrocardiograms, were asked to interpret the same group of 100 tracings on two different occasions. Complete agreement was present in only one-third of the reports, and major agreement in about one-half. Even more disturbing perhaps was the fact that when the same tracings were read on the second occasion by the same readers, one record out of the eight, on the average, was reported differently. This paper surely indicates that electrocardiographic reports should not be regarded too seriously, especially when they are in conflict with other clinical findings.

PHYSICAL DIAGNOSIS AND DIAGNOSTIC PROCEDURES

The use of graphic methods for the registration of heart sounds, murmurs, and other vibratory phenomena has continued to interest many workers Luisada *et al* (49) report studies on dogs and man which they interpret to support their belief that the central, major high-frequency components of the first heart sound are caused by sequential closing of the mitral and tricuspid valves, followed by opening of the pulmonic and aortic valves. Leatham (50), on the other hand, has suggested that the major high-frequency components of the first sound, often responsible for splitting, are caused by closure in sequence of the mitral and tricuspid valves with opening of the semilunar valves playing little or no role in its genesis. Studies by Reinhold & Rudhe (51) based, to a considerable extent, on electrokymograms support Leatham's view.

Leonard and his associates (52) point out that the presystolic extra sound may migrate toward the first sound and disappear when tourniquets are placed on the four extremities of a patient with an extra sound of this kind, and some of the factors involved in the production of atrial gallop sounds are discussed The same group of workers (53) have also published a more general excellent discussion on gallop rhythm.

Leatham (54) points out the differences between systolic murmurs of the ejection and regurgitant types The latter are pansystolic in time and are commonly caused by mitral or tricuspid insufficiency and by interventricular septal defects The former are separated from the first sound and tend to have the diamond shape (in sound tracings) with termination before the second sound They are found in typical form in aortic and pulmonic stenosis, but it is likely that many functional murmurs are of this general character.

Schilder & Harvey (55) emphasize the importance of the recognition of

the murmur of tricuspid insufficiency in patients with severe mitral stenosis. If this murmur is wrongly attributed to mitral insufficiency, mitral surgery may be denied to a patient who would benefit greatly from the procedure The murmur of tricuspid insufficiency is usually loudest medial to the apex and is accentuated by inspiration, whereas the murmur of mitral insufficiency is ordinarily loudest at the apex and is less loud with inspiration.

Barlow & Shillingford (56) have shown that the inhalation of amyl nitrite causes a temporary decrease in the loudness of the murmur of mitral insufficiency with a fainter second sound, whereas the murmur of aortic stenosis becomes progressively louder as the effect of the drug reaches its peak. This test may be very helpful, especially in patients in whom the nature of an apical systolic murmur is in doubt. Bruns & vander Hauwaert (57), in a study of systolic murmurs at the aortic area in patients in older age groups, found that many of these individuals had deformities of the aortic valve caused by sclerotic lesions without significant obstruction. This study emphasizes the fact that in old age many loud but functionally innocent murmurs arise at the aortic valve, whereas in childhood and youth physiologic (functional) systolic murmurs are produced in the right ventricular outflow tract Neill & Mounsey (58) point out changes in the murmur arising from a patent ductus arteriosus with alterations in the pressure in the pulmonary artery. When this pressure was not significantly elevated a continuous murmur was present, but when the pressure equalled or exceeded that in the aorta the continuous murmur was replaced by a relatively soft systolic murmur These authors also describe differences between the continuous murmur of an open ductus and those attributed to other causes.

Registration of auscultatory phenomena within the right heart by a special transducer at the end of a catheter is described by Lewis *et al.* (59). The authors believe that the technique involves no greater risks than are usual with catheterization of the right heart, that it may increase our knowledge of the origin of cardiac sounds and murmurs and may be helpful in the diagnosis of congenital lesions Luisada & Liu (60) describe the use of a column of saline within an ordinary catheter for intracardiac use as a wire to permit the registration of intracardiac electrocardiograms, and also as a medium for the transmission of sonic vibrations from the inside of the heart to the outside The authors believe that with a suitable differentiating circuit and filters faithful reproduction of the vibrations existing at the end of the catheter within the heart is possible.

Groom & Sihvonen (61) describe a technique for recording movements of the surface of the body over the precordium or elsewhere which involves the use of the skin as one plate of a condenser Movements of the skin surface alter the capacitance of the condenser and, with suitable associated apparatus, these changes in capacitance, which are proportional to motion of the skin, are recorded. Since air conduction of sound waves is not involved here, the device is insensitive to extraneous noise, and it may also be used to record either gross low-frequency movements of the precordium or, with suitable

high-pass filters, vibrations in the audible spectrum may be registered. The authors emphasize the point that with the high sensitivity possible, systolic murmurs which are inaudible with an ordinary stethoscope may be recorded. This feature of the instrument is of considerable scientific interest and its proper use may help in unraveling some problems in the genesis of murmurs The reviewer, however, shudders to think what might happen if this device should fall into the hands of charlatans.

Harrison *et al.* (62) have continued with studies of low-frequency movements over the precordium, employing a combined mechanical and piezoelectric device described earlier (63). In this work movements believed to be of atrial origin were investigated, and it is believed that the right atrium causes small outward movements to the right, and the left atrium backward movement to the left. Such movements were absent in patients with atrial fibrillation and were accentuated with cor pulmonale and mitral stenosis, respectively. The authors do not state whether any of the movements described can also be picked up by careful inspection or palpation. The reviewer believes that one of the greatest values of devices, like the one employed in this study, is that they indicate findings which may be appreciated with careful physical examination.

A correlation of left atrial border movements, recorded by the electrokymograph, with volume variations and pressure tracings from this chamber done by Judge and his colleagues (64) suggests that the former are usually altered in a characteristic fashion in predominant mitral insufficiency. The rapid inward movement of the atrial wall in the early period of diastole (atrial emptying) was found to be particularly important.

Laconi (65) reports studies of left ventricular border movements done with a special roentgenkymographic technique which he believes may give more consistent and reliable results in patients with constrictive pericarditis than when border movements are recorded with the electrokymograph. The reviewer is not qualified to evaluate the correctness of this opinion but does know that occasional patients with coronary artery disease and diffuse myocardial degeneration, like that seen with primary amyloidosis, may have abnormal precordial pulsations identical with those seen in constrictive pericarditis.

Several groups have been interested in arterial pulse tracings, especially in relation to aortic stenosis. Hancock & Abelmann (66) have recorded such tracings with a needle in the brachial artery in 250 patients and normal subjects and found that, although expected changes in the form of the records were found in most patients with aortic stenosis, aortic insufficiency, and several other conditions, similar changes occurred occasionally in their absence. Further, the degree of aortic stenosis was not always reflected by the pulse tracing. They felt that further studies of the form of the pressure changes in the aorta in various conditions and the factors which may alter the pulse wave as it is transmitted peripherally, must be carried out. Fleming (67) has recorded pulses from the left ventricle and aorta in a number of

patients undergoing surgery for aortic stenosis and other conditions in which the stroke volume of the left ventricle was altered. These studies indicate that the aortic pressure tracing may show an anacrotic notch or a definite double peak (pulsus bisferiens) clearly related to the period of greatest flow from the left ventricle and that these phenomena are probably caused by a suction (Venturi) effect, as was suggested by Katz *et al.* (68) many years ago. The presence of a pulsus bisferiens was felt to contraindicate aortic valve surgery, and Fleming's findings (67) help greatly to explain the variability in the form of the brachial pulse reported by Hancock & Abelmann (66). Doyle & Neilson (69) describe the use of the Valsalva maneuver in studies of the femoral arterial pulse as a guide in determining the severity of aortic stenosis.

Ballistocardiography has been the subject of many studies in recent years and, due largely to increased knowledge and more agreement regarding purely technical aspects of the procedure, it seems to the reviewer that some order is appearing in this previously chaotic field. Thus, the differences between displacement, velocity and acceleration records, and the variables (and artefacts) introduced by different types of supporting media are beginning to be appreciated. Scarborough & Baker (70) give an authoritative and sane discussion of the many technical problems involved in ballistocardiography and express optimism regarding the clinical value of the records as further information and experience is gained. The authors point out the need for carefully controlled experimental studies on animals, and Scarborough (71) describes ballistocardiograms taken on dogs under morphine-barbiturate anesthesia. An ultra-low frequency suspension for the animals was employed, and acceleration curves were recorded. Although records similar to those obtained in normal human subjects were obtained, many of the tracings were of "abnormal" form, particularly as experiments progressed. Abdominal compression of the animals caused the records to become more normal, suggesting that pooling of blood in the splanchnic area, caused by the anesthetic, was an important factor in the deterioration of the tracings. Using a similar technique, Honig & Tenney (72) compared the ballistic records of 20 normal adults with 4 individuals with normal hearts but with absence of both lower extremities In addition, two of these had complete or partial absence of the arms. The measured reaction force in the limbless subjects was considerably greater than in the normal individuals studied, and this was believed to reflect freedom from impedance of the limbs. This, in turn, suggested that an instrument capable of recording motion of the thorax alone would be desirable.

Mahl & Lange (73) compared the usual methods for estimation of circulation time, employing Decholin and saccharin, with an objective method involving the intravenous injection of 3 cc of 5 per cent fluorescein solution

in patients with congestive heart failure, and not only suggest that an objective method is desirable but point to the need for some scepticism when the circulation time obtained with the use of Decholin or saccharin is not in line with other clinical impressions.

Much work involving the use of dilution curves, usually employing suitable dyes, has been done to aid in the diagnosis of shunts within the heart and in the investigation of other congenital and acquired defects. Grant *et al.* (74) discuss electrocardiographic findings, blood gas analysis (employing nitrous oxide), selective angiocardiography, and dye dilution methods in the diagnosis of left to right shunts. The authors present data indicating that small shunts of this kind may be recognized by means of the nitrous oxide technique when they cannot be detected with certainty from estimation of oxygen saturations alone, and also point out the value of dye dilution curves in the location of left to right shunts if the dye is introduced through a catheter into one or more sites. The nitrous oxide test and its advantages are discussed in detail by the same workers in a paper by Morrow and his associates (75) Falhot & Fabricius (76), however, using a similar technique, believe that dye dilution curves only rarely give information not obtained by simple catheterization or angiocardiograms.

Shillingford (77) describes a simple method involving the injection of Evans blue dye into the right atrium or pulmonary artery and the registration of a dilution curve with a photoelectric device on the ear, which he believes gives a fairly accurate estimate of the amount of mitral insufficiency that is present. The presence of such a lesion causes a delay in the fall of the curve, and this increased spread (measured arbitrarily at one-tenth of the maximum concentration) divided by the appearance time gives a ratio which seems to be proportional to the amount of regurgitation that is present Braunwald & Morrow (78) describe an interesting technique for detecting and estimating the degree of aortic insufficiency in man. Indigo carmine dye was injected slowly into the aorta at various levels through a catheter passed upward from the femoral atery, and dilution curves were recorded by a photoelectric sensing device on the right ear In subjects without aortic regurgitation, the dye injected immediately distal to the arch caused no dye to appear in the ear during its primary circulation, but with this lesion, dye injected at lower levels produced an immediate response. Sekelj *et al* (79, 80) describe an automatic electronic computer for estimating the concentration of Evans blue dye in arterial blood and describe its application in the measurement of cardiac output by the dilution technique. Although the instrument is quite complicated, the authors believe it will greatly simplify the technical procedure and permit rapid and accurate quantitative estimation of the concentration of the dye in arterial blood.

Goodwin & Sapirstein (81) describe an experimental study in dogs in which dilution curves, obtained by an electrical conductivity technique, were found following a single intravenous injection of autogenous plasma The advantages of the method compared with previously described conductivity

techniques were pointed out and estimations of cardiac output were found to agree closely with those obtained using dyes for the dilution curves.

Comparison of wedge pressures with those recorded directly from the left atrium by Murphy (82) led to the conclusion that the former may provide a very poor estimate of the true left atrial pressures, especially when the latter are elevated. Paul & Rudolph (83) point out that the obstruction of a stenotic pulmonic valve by the catheter during right heart catherterization may produce acute symptoms and that possible serious consequences may be prevented by awareness of this possible danger.

ARRHYTHMIAS

Interference dissociation is considered by many cardiologists as one of the rare and complicated arrhythmias; even the term has been poorly understood and has been used to designate different types of disturbances by different authors. Miller & Sharrett (84), in a long review type of article, clarify many features of the arrhythmia and classify the multiple disturbances which logically fall into the category of interference dissociation, as they define it. They believe that it is characterized by the existence of two different foci in any part of the heart which elaborate impulses causing excitation to spread in opposite directions toward the two foci, which results in more or less complicated interference phenomena usually of a repetitive nature. They further point out that "heart block predisposes to, and frequently complicates, interference dissociation."

Experimental production of extrasystoles in dogs by the application of veratrine and inhalation of 20 per cent carbon dioxide and 80 per cent oxygen was carried out by Scherf *et al.* (85). It was then found that warming the area of the origin of the premature beats shortened, and cooling lengthened the interval between the previous normal response and the ectopic beat. These results were believed to indicate that the extrasystoles were caused by a "phenomenon of after-discharge in an altered cell."

Marriott & Bradley (86) present electrocardiograms from three patients which they believe, show premature beats arising in the main stem of the His bundle, and express the opinion that such beats are not as rare as has been usually thought. They point out, quite correctly, that such premature beats cannot be identified with complete certainty, since an ectopic beat arising in the A-V node, without retrograde stimulation of the atria, would cause an identical electrocardiogram.

Pick & Dominguez (87) point out the existence of a nonparoxysmal A-V nodal tachycardia in which the rate is relatively slow (70 to 130 per min.) and which is not associated with abrupt onset or termination of the attacks. This type of rhythm disturbance occurred usually with digitalis intoxication, acute rheumatic fever, and posterior myocardial infarction.

Langendorf (88) describes the alternation of A-V conduction time occurring most commonly with first degree A-V block or with 2:1 or 3:1 block and believes that this peculiar type of conduction is one of the most

frequent manifestations of the supernormal phase of conduction. Eldridge (89) describes an example of probable reciprocal beating of the atria in a patient with partial A-V block and points out that the hypothesis of dual conduction in the A-V node suggested by Moe and his associates (90) provides a logical explanation for reciprocal rhythm. Goldman (91) suggests that treatment with quinidine and procaine amide in combination is more effective than either drug alone in the restoration of normal rhythm in patients with atrial fibrillation.

CONGENITAL HEART DISEASE

In the field of congenital heart disease much material relating directly to techniques of surgical treatment has appeared, and this cannot be covered here. Two reports (92, 93) of stenosis of the pulmonary arteries distal to the pulmonic valve emphasize the relative frequency of the occurrence of peripheral pulmonic stenosis. Most of the patients, proved to have such defects either by right heart catheterization or by angiocardiograms, also had other congenital heart lesions. A continuous murmur occasionally occurs as a result of such stenosis and may be a helpful sign.

Grant (94) discusses a group of patients who must be differentiated from those with a complete mirror-image dextrocardia and those whose hearts are displaced to the right by some extrinsic cause This group is classified as having dextroversion of the heart and is characterized by a rightward rotation of the ventricles, with the atria remaining in their normal positions These patients usually have defects in other thoracic and abdominal organs, as well as additional cardiac malformations.

Brotmacher & Campbell (95) discuss the natural history of patients with simple interventricular septal defects, and also a group in which the ventricular septal defect is accompanied by pulmonic stenosis In the former, the authors believe that patients should be classified on the size of the defect, the direction of the shunt, and the level of the pulmonary arterial resistance and, further, that the terms maladie de Roger and Eisenmenger's complex should be dropped. In the group having both interventricular septal defects and pulmonic stenosis, the close relationship to patients with the tetralogy of Fallot is pointed out, together with the fact that the presence of the stenosis may decrease the size of the left to right shunt (which would otherwise exist) and thereby prevent marked pulmonary changes and hypertension from developing. Essentially, the same conclusions were reached by McCord and his associates (96) in a study of patients with the tetralogy of Fallot They point out that the clinical state of such individuals depends primarily on the size of the septal defect and the degree of pulmonic stenosis, and feel that the time-honored term, the tetralogy of Fallot, has outlived its usefulness.

Brotmacher (97) made some interesting studies to determine why children with congenital heart disease of the cyanotic type often crouch in a squatting position. His observations were made with normal subjects and

with patients suffering from congenital heart disease, both at rest and during recovery from exertion. In the former circumstances he found that squatting reduces the blood flow to the legs, thus increasing that to the upper part of the body. In addition, although the oxygen content of arterial blood is not changed, that of the venous blood (and therefore capillary and tissue oxygen tensions) is increased, resulting in better oxygenation of vital centers in the upper part of the body. During recovery from exercise, again squatting reduced blood flow to the legs, but this was believed to result largely from obstruction of the venous return from the lower extremities. This obstruction, in turn, limited the amount of very poorly oxygenated blood returning to the right heart during this critical period.

Kelly & Lyons (98) report a study of 19 patients over the age of 47 years with atrial septal defects The oldest of this group was a male of 76 years, still in fairly good health. This report emphasizes that patients with such defects may live long and active lives much more often than is true of the other common congenital lesions. The authors also point out the common physical, electrocardiographic, and roentgenographic findings in this condition and believe that the diagnosis can usually be made on the basis of the clinical examination alone. The common complications, namely frequent respiratory infections which often cause chronic lung disease, and pulmonary hypertension leading to right heart dilation and failure often with a right to left shunt, are discussed. An uncommon but serious complication was thrombosis of the pulmonary artery.

Bruce & John (99), in studies on the effect of change in position and exercise on pulmonary hemodynamics, found that patients with uncomplicated atrial septal defects showed a significant increase in pulmonary flow without change in pressure, with exercise in the upright position, and were less likely to develop desaturation of arterial oxygen than were patients with interventricular septal defects. These and other observations may be of diagnostic help.

One of the most troublesome and controversial questions related to congenital heart disease is the problem of the factor or factors which lead to irreversible structural changes in the pulmonary arteries with increased resistance in the pulmonary circuit and, often, progressive pulmonary hypertension. Studies in infants and young children by Ferencz & Dammann (100) suggest that lesions which obstruct the pulmonary venous return may be important in this connection

Mayer and his colleagues (101) discuss clinical and laboratory findings in 10 patients with Ebstein's anomaly and correlate their data with that obtained by other investigators. The importance of the clinical recognition of this condition is stressed, since definite risks, usually related to serious arrhythmias, attend cardiac catheterization and surgical procedures done on these patients

Linde *et al.* (102) report the value of angiocardiograms in the diagnosis of endocardial fibroelastosis. The characteristic finding was the unchanging size and shape of the left ventricle.

RHEUMATIC HEART DISEASE

Many of the studies in the field of rheumatic heart disease are concerned in one way or another with surgical procedures for the treatment of valve lesions. Although the reviewer marvels at the great progress in this work and the unquestioned benefits that many patients with rheumatic valve lesions, especially mitral stenosis, have obtained from cardiac surgery, he does not think that a surgical approach will ever be more than partial and palliative treatment for this large and important group of patients. The only complete solution to this problem will be found in the prevention of acute rheumatic fever and particularly the cardiac involvement which so often accompanies it. In this connection, the work of Rammelkamp and his co-workers, well-summarized in the Lewis A Conner Memorial Lecture given by Rammelkamp (103) in 1957, is of great interest. These workers point out that not only is Group A streptococcal infection clearly related to rheumatic fever but present evidence indicates that such infection persists during periods of rheumatic activity, and indeed may be responsible for long continuing bouts of rheumatic fever during which serious valvular and myocardial damage may occur. If such streptococcal infection can be eradicated early in the course of rheumatic fever by an adequate course of penicillin, the benefits are pretty obvious.

Harris *et al.* (104) report studies on a small group of children known to have had rheumatic fever in the past who developed new murmurs during a period when all laboratory studies (sedimentation rate, C-reactive protein, antistreptolysin titres) were normal. The finding of a new murmur was considered to be evidence of rheumatic activity in these patients. In view of the many factors which may lead to the appearance (or disappearance) of heart murmurs, the reviewer has some doubt about the correctness of the conclusions of the authors.

Evans & Short (105) point out, on the basis of pathologic studies, that patients with mitral stenosis and pulmonary hypertension may have a diffuse process involving the small arteries and arterioles throughout the lungs. These vesssels are constricted, inelastic, and show intimal proliferative changes. The authors further discuss the difficulties which often arise in the certain diagnosis of mitral stenosis in this group of patients and express the opinion that the vascular changes in the lungs are probably progressive and irreversible and therefore mitral valvulotomy is unlikely to produce great or lasting benefit.

Ito and his associates (106) describe the development of a syndrome identical to the "postcommissurotomy syndrome" occurring in 13 of 24 patients who underwent intrapericardial surgery for correction of various con- [illegible]

the result of a traumatic pericarditis and think the similar picture, occurring after mitral surgery, is of the same character and not related to reactivation of rheumatic fever.

Soulié and associates (107) and Belcher (108) discuss restenosis of the mitral valve following commissurotomy. These workers agree that the common cause for restenosis is inadequacy of the original procedure but that a "true" restenosis may occur as the result of recurrent rheumatic and possibly nonspecific infections. Generally speaking, the results following reoperation have been good.

Studies by Wilson & Lim (109) and Magida & Streitfeld (110), on the natural history of rheumatic heart disease in the age group from 20 to 50 years, bring out many factors that are important in connection with mortality and morbidity during this period. The presence or absence of marked cardiac enlargement at the age of 20 years had great bearing on survival during the subsequent years. Recurrent rheumatic carditis, atrial fibrillation, bacterial endocarditis, pregnancy, pneumonia, and embolic phenomena were important factors in both mortality and morbidity.

CORONARY ARTERY DISEASE

The most important work in connection with coronary artery disease is, of course, related to its etiology and, since the big field of atherosclerosis is not included in this review, only a limited number of articles will be considered here.

A follow-up study on patients with one or more myocardial infarctions by White, Bland & Levine (111) illustrates many matters of importance in the prognosis and management of these individuals. The completeness of recovery at the end of one month after an acute infarction was found to be the best guide in prognosis. This study also emphasizes the importance of and justification for an optimistic attitude on the part of the physician.

Experimental studies on pigs by Paul and his associates (112) indicate that extensive intercoronary collateral circulation develops following the ligation of coronary arteries, and that this may develop to a significant degree in two days In control animals intercoronary anastomoses were rare.

James & Burch (113, 114), using an injection technique, studied the coronary arterial distribution in the atria and in the ventricular septum in normal human hearts The latter structure was found to be nourished primarily from the anterior descending branch of the left coronary artery, and it was felt that the septum "is an important site of collateral channels in the human heart."

Patients who had the surgical creation of an arteriovenous fistula between the descending aorta and the coronary sinus (Beck II, revascularization procedure) were shown by Moir & Pritchard (115) to have an increase in cardiac output and work, and a decrease in the effective systemic flow and peripheral resistance. Heart failure which could be reversed by obliteration of the shunt occurred in some of the patients. Similar dismal results, in three

fants with an anomalous left coronary artery arising from the pulmonary artery, blood flows through extensive anastomotic channels from the normal right coronary artery directly into the anomalous vessel and into the pulmonary artery. This means that the left ventricle receives essentially no blood, and led the authors to suggest that ligation of the anomalous artery at its origin should be a lifesaving procedure, since both ventricles would be then nourished by the right coronary artery.

Twenty-four patients with coronary artery disease were studied by Müller & Røvik (118) by right heart catheterization to study the effects of anginal pain, physical activity, and nitroglycerin on the cardiac output, pulmonary capillary pressure, etc. The results of the study were much as one might expect, although by using the pulmonary capillary pressure as an index of left ventricular failure or competence, it was found that signs of left heart failure developed before anginal pain appeared whether the angina occurred spontaneously or was induced by exercise. Nitroglycerin improved the work capacity of the left ventricle, possibly by increasing coronary flow. The authors make no comments about any danger connected with right heart catheterization in patients with coronary disease, but it is the opinion of the reviewer that the risks of the procedure are considerable in this group and that it should not be done unless there are special indications for it.

Riseman *et al* (119) present a good discussion of the use of nitroglycerin and other nitrites in the treatment of angina pectoris. Of particular interest is the report that drugs like erythrol tetranitrate and mannitol hexanitrate were much more effective when used sublingually than by the oral route. Cossio (120) reports relief of pain in patients with angina pectoris and a few individuals with intermittent claudication from iproniazid and isoniazid. He believes that these drugs, especially the former, are highly effective in preventing pain caused by ischemia and believes that the drugs act by depressing oxidative enzymes in the heart and thus either increase the utilization of oxygen or decrease the amount that is required for essential metabolic processes in the myocardium.

MISCELLANEOUS

Observations by Armen and associates (121), on a large group of patients with chronic pulmonary disease and secondary cardiac involvement, point out the difficulties in the early diagnosis of cor pulmonale in such individuals, and particularly the inconsistency of electrocardiographic changes In only 27 per cent of the patients were electrocardiographic changes characteristic of right ventricular hypertrophy found, and cor pulmonale of advanced degree was present in some of the patients with only mild nonspecific changes in the tracings The need for combined clinical, radiologic, and electrocardiographic evidence for the diagnosis of pulmonary heart disease was emphasized.

Problems in the diagnosis of primary pulmonary hypertension, and particularly of other conditions which may simulate this, are well discussed by

Branchfeld and associates (122). The importance of excluding mitral stenosis by left heart catheterization is emphasized.

Eleven patients with diffuse myocardial fibrosis arising from coronary artery disease, old myocarditis, tuberculosis, or unknown causes were discussed by Robin & Burwell (123). It was emphasized that the hemodynamic as well as the clinical findings in these patients closely resemble those seen with constrictive pericarditis, endocardial fibroelastosis, and other conditions like primary amyloidosis, which may cause diffuse involvement of the myocardium.

Two patients with proved and one with probable myocardial fibrosis were studied by Nye *et al.* (124), with conclusions much like those reached by Robin and Burwell. All three of these patients were erroneously considered to have constrictive pericarditis and had thoracotomies which revealed a normal pericardium. Some differences in the pressure tracings obtained in the right atria and ventricles in these patients compared with those observed in patients with proven constrictive pericarditis are pointed out, and it is suggested that these quantitative differences, if found by further studies to be constantly present, may help in the differential diagnosis.

Teare (125) reports an unusual type of asymmetrical hypertrophy in the hearts of eight fairly young adults, with sudden death occurring in seven. The pathologic findings were "bizarre and disorganized arrangement of muscle bundles associated with hypertrophy of individual muscle fibers and their nuclei."

Three patients with myxomas of the left atrium are reported by Jackson & Garber (126) and five similar patients by Harvey (127). Both of these papers emphasize that, since surgical treatment for intracardiac lesions is now available, the recognition of these tumors is important. The variability of symptoms and signs with change in position, the resemblance to mitral stenosis in some patients, and the value of angiocardiograms in diagnosis are pointed out

A very interesting and important article by Burton (128) on the importance of the size and shape of the heart illustrates the application of the law of Laplace in explaining why certain areas of the ventricular walls are thinner than others, why the dilated heart is at a great mechanical disadvantage compared to the heart of normal size, and especially why the large fraction of the total work load of the heart involved in maintaining necessary tension in the ventricular walls (rather than doing any external work) is so important Burch and his colleagues (129) and Burch (130) had discussed these matters from slightly different points of view earlier but, as Burton points out, few cardiologists have paid any attention to these very basic considerations.

Bain *et al.* (131) review the problem of subacute bacterial endocarditis arising from structures in the right heart from both the clinical and pathologic standpoints Many interesting points are discussed, but of special significance in diagnosis was the fact that only 35 per cent of the patients

had heart murmurs. Usual signs of infection, anemia, positive blood cultures, microscopic hematuria, and evidences of pulmonary infarction were most helpful in diagnosis. Splenomegaly, recognizable clinically, and evidences of peripheral emboli were less common than with left-sided bacterial endocarditis.

Zoll *et al* (132) recommend the slow intravenous administration of epinephrine or isoproterenol in dilute solutions for patients with persistent ventricular standstill or frequently recurring episodes of standstill or marked slowing of the ventricles This type of treatment is often useful in connection with external electrical stimulation.

Fletcher & Brennan (133) discuss the use of digitalis in patients with intractable heart failure and believe the acetyl strophanthidin test may be very valuable in regulating the dose of the drug. They also believe that combined therapy with digitalis and potassium may be desirable in selected patients.

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CARDIOVASCULAR DISEASES (ATHEROSCLEROSIS)[1]

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In 1908, Ignatovski, of the Imperial Military Medical Academy, St. Petersburg, announced that atherosclerosis developed swiftly in rabbits fed egg-yolk and milk. In 1958, thousands of animals, from chicks to baboons, were used in North America in experiments relating arterial disease, both atherosclerotic and thrombotic, to diets rich in saturated fat and cholesterol Between 1908 and 1913, Stuckey, Chalatov, and Anichkov, all working in the Imperial Military Medical Academy, proved that the lipide content of the diet, and notably its cholesterol content, was the determinant of disease in rabbits The Russian studies were confirmed in San Francisco in 1915, a few months after Anichkov's work was known, but in 1957–58 committees of several learned societies in the United States declined to accept the theory that diet played a decisive role in vascular disease in man. Further study was urged.

The oldest theory, that of Rokitansky, blames all atherosclerosis on thrombosis and organization of thrombi adherent to vessel walls. This still has persuasive proponents (1, 2, 3), and there are some who see thrombosis as part of a dual etiology (4). There is great regional variation in what pathologists find in occluded coronary arteries In the United States, hemorrhages into atheroma are frequent and occlusion often occurs without thrombosis (5, 6), while in England and Canada thrombosis is usually found (1, 2, 7). The experimental production of coronary and renal arterial thrombosis, by diets even richer in saturated fat and cholesterol than those needed to cause atheroma (8 to 11) brings Rokitansky's theory into alignment with Ignatovski's.

Virchow's theory that atherosclerosis arises from degeneration of the intima is still upheld by Holman (12, 13), and others (14). It is supported only by the fact that intima, like all other tissues, can form cholesterol from tagged acetate, and phospholipide from tagged phosphate (15). The proponents of this theory now concede that diets rich in fat may alter the rates of intimal formation of cholesterol, or delay its degradation, but they regard the lipide as being locally produced, not as infiltrate from plasma. Thus, human atherosclerosis is considered a process like that causing cholesterol-rich granulomas in Hand-Schuller-Christian disease and related disorders of bone and reticuloendothelial systems Followers of Rokitansky and Virchow reject any relation between human atherosclerosis and the animal disease evoked by modifications of Ignatovski's experiments.

Accumulation of carotenoid pigment has been noted in aging atheromas

[1] The survey of the literature pertaining to this review was completed in July, 1958

(16). Sphingomyelin is abundant in β-lipoprotein and a major component in older atheromas (17). Peterson has reported that atheromas, like β-lipoproteins, are relatively poor in lecithin as compared with whole plasma, and that diabetics, with a high ratio of cephalin to sphingomyelin in plasma, also have a high ratio in their atheromas (18, 19). The phospholipides could be synthesized in the atheromas in the same ratios as found in β-lipoprotein, but the carotenoids must come from plasma and eventually from the diet

There have been numerous additions to the reports that patients with coronary disease have a higher level of blood cholesterol (20, 21) or a higher level of β-lipoprotein (22), or a much higher level of Dangerfield's pre-β-fraction (23, 24, 25) than do controls of the same age and sex. The pre-β-fraction, unlike β-bound cholesterol, is not extracted from the paper strip by ethanol.

Regional or ethnic variations in severity and site of atherosclerotic lesions continue to be reported, many authors relating severity to plasma cholesterol levels and diet (26 to 31). There are also additional reports that blood cholesterol levels in man can be raised by increasing the dietary intake of saturated fatty acid and lowered by substituting starch, fatty acid with a single double bond (mono-ene acids such as oleic), and especially by substituting fatty acids with two or more double bonds (poly-ene acids such as linoleic) in equal caloric quantities (32). This has led to further animal experiments, and it has been shown that increasing the dietary ratio of saturated to unsaturated fatty acid will either potentiate the effect of added cholesterol (33) or, even in rabbits, produce high plasma cholesterol levels and atherosclerosis on cholesterol-free diets (34). This is strong support for the theory that diets rich in animal fat raise blood lipide, and that plasma rich in lipide, and especially in the fraction carried by β-lipoprotein, permeating the intima will eventually lead to atherosclerosis (35).

Rutstein and his colleagues have found that tissue cultures of human aortic intima are sensitive to the presence of cholesterol and of saturated fatty acid added to the medium which supports growth Additions of ethanol, in concentrations equal to that of the cholesterol solutions which had been used, had no effect and the cells showed scarcely any Sudanophilic material even when cholesterol, 1 mg. per cent, or β-lipoprotein with 30 mg. per cent cholesterol, was added. But cholesterol at 3 mg. per cent, or β-lipoprotein providing 50 mg. per cent cholesterol, caused definite cellular swelling and appearance of lipide droplets. These became marked with 5 mg. per cent cholesterol, or 70 mg per cent cholesterol in β-lipoprotein. The changes were accentuated by adding 1 mg per cent stearic acid (saturated), and inhibited by 1 mg. per cent linolenic acid (two double bonds) (36). This extends

observed in rats fed fully hydrogenated lard, palmitic or stearic acids, or ethyl stearate (39).

Other deleterious effects on the circulatory system of diets rich in fat of any degree of unsaturation, are acceleration of the clotting mechanism (40, 41, 42) and impairment of oxygen diffusion into and out of the red cells (43). The latter, by increasing gradient of oxygen tension from alveoli to erythrocyte, causes postprandial fall in arterial saturation, and probably an even greater degree of tissue anoxia, thus causing angina after high fat meals, (43).

While observers differ as to which tests of coagulability are most altered by high fat diet, they agree in finding no specific effect of saturated fats. On the other hand, fibrinolysis is apparently markedly retarded by diets rich in saturated fats but unaffected by similar levels of unsaturated fats (11). Hartroft's group, investigating the basis for the fall in postoperative thrombo-embolism in occupied Norway (45), found that diets rich in saturated fat prevented lysis of clot emboli injected into lungs of rodents When saturated fats were fed in abundance to rats receiving cholesterol and thiouracil to cause hypercholesterolemia, they often showed spontaneous thromboses of arteries, with renal and myocardial infarction (9, 10). Corn oil, given in similar amounts, was never effective in causing thrombotic disease in such experiments Thus, it is probable that thrombotic arterial disease, as well as thrombo-embolic disease of the veins, may be conditioned by diet and occurs when the amount of saturated fat is unusually high or susceptibility unusually great.

In dissent from the view that there is a consistent relation between the saturated fat content of the diet and coronary atherosclerosis, reviews of dietary fat and cardiac death rates in many countries emphasize numerous exceptions (46, 47). One report states that there was no relation between blood cholesterol levels before death and severity of coronary lipide infiltration at necropsy (48) Similar variability was noted in both coronary and aortic disease in rabbits with hypercholesterolemia caused by diet (49). There also is great variability in blood cholesterol levels reported by different laboratories on single blood samples, in one study seven laboratories gave values of 180 to 312 mg. per cent for one plasma, 312 to 498 for another (50).

Emphasis on the many variables which influence the effect of diet on plasma cholesterol, and on deposition of lipide or thrombi at given sites, was the theme of many reports. Outstanding was Myasnikov's (51) summary of recent Russian work on rabbits, by the pupils of Anichkov working in his Moscow laboratory Feeding ascorbic acid or barbiturate decreases the plasma cholesterol and atheroma formation in rabbits on cholesterol-enriched diets; vitamin D, caffeine, and amphetamine increase both plasma lipide and atherogenesis (51) Exercise decreases plasma lipide and atherogenesis, but vigorous effort to exhaustion leads to myocardial damage in

rabbits with coronary atheroma (51). Dicumarol increased atherogenesis but had no effect on blood cholesterol, while heparin reduced atherogenesis more than would have been anticipated from its effect in lowering plasma cholesterol (51).

In comparing patients with recent coronary attacks and control subjects, Keen in England found the former had diets which provided not only a higher per cent of calories from fat, but more calories, proteins, and carbohydrate, than the controls (52). Albrink found that coronary patients have a level of plasma triglycerides which is higher than controls, the percentage difference exceeding that of the plasma cholesterol differences. The triglyceride level does not fall, and may rise, on diets which reduce plasma cholesterol (53). In comparing coronary patients with controls, the serum iodine number was found by Leupold to be 50 per cent higher in the patients, though the cholesterol levels were only 10 per cent higher than the controls. On diets enriched with linoleic and linolenic acids, a group of the coronary cases showed a fall of cholesterol from 261 to 192 mg per cent, with a decrease in iodine number from 1312 to 871. The iodine number of the controls was 705 (54). The fall in plasma iodine number on a diet enriched by unsaturated fatty acids is even more surprising than finding higher iodine numbers in the patients This report is in conflict with actual determinations of fatty acid composition of plasma showing the same proportion of saturated and unsaturated acids in coronary cases and controls (55).

When given radioactive fat meals, coronary patients showed higher peaks and longer persistence of the material in the plasma (56). The level of the Sperry enzyme, which catalyzes the esterification of cholesterol, was found to average 33 units in plasma of coronary patients, 41 in controls, and was lowest in idiopathic hyperlipemia, 22 units (57).

Heparin, plasma lipides, speed of coagulation, and speed of clearing chylomicron turbidity of incubated plasma are all interrelated, although most studies take up only one facet of the problem Thus, it was found in one study that the titer of lipoprotein lipase cofactor declined with age in the plasma of normal men, but was reduced 32 per cent from control levels in coronary patients when sesame oil emulsion served as substrate, 18 per cent with washed chylomicrons (58). It was lowest immediately following infarction, rising slowly during convalescence. Heparin is a known cofactor for this system, and a low level of "heparin," meaning that material giving some of the colorimetric reactions of heparin, has been noted in the serum of coronary patients, as compared to that of the controls (59). An inverse relation of "heparin" to cholesterol and the lipoproteins rated S_f 0–20 in Svedberg ultracentrifugation also has been noted (60).

Coagulability of blood, following intravenous injection of heparin, returns to normal much more swiftly in patients with coronary disease than in controls (61). Titration of serum for "heparin antagonist" showed higher levels with advancing age (62, 63, 64), slight increase in arteriosclerotic subjects in one series (63), none in coronary patients, nor in diabetes or nephro-

sis, in another (64). In these studies the effect of the plasma on clearing when mixed with active plasma and substrate was tested; in another, the antagonism to clearing, using plasma obtained after heparin injection, was greater in hyperlipemic subjects than in normals (65). The injection of heparin in dogs, during the intravenous infusion of olive oil emulsions, caused immediate lowering of plasma cholesterol, and hastened the fall in plasma fatty acid (66). Accelerated clearing of alimentary hyperlipemia was noted after high fever induced by pyrogens, but as it was blocked by protamine (as heparin clearing is blocked), it was assumed that the fever released heparin in the animals (67). Plasma levels of heparin and of heparin antagonists may be of great importance in explaining the rise in plasma cholesterol and in risk of thrombosis which accompanies aging.

Although there have been past reports that a fatty meal causes accelerated coagulation (40, 41, 42, 68), and ethenolamine, but not triglyceride, cholesterol, or lecithin, has been found to accelerate coagulation (69), some observers fail to find any effect on coagulation, using sensitive techniques (70, 71). In a group of coronary patients on the fat-free, rice-fruit diet, there was no change in most indices of coagulation, but platelet stickiness was reduced (72) Capillary flow was abnormal, with "sludging" of red cells, 6 hr. after a high-fat meal (73)

Keys reported new proof on the efficacy of polyunsaturated fats in lowering, and of saturated fats in raising blood cholesterol, with monounsaturated fats having no effect (74; 75). The value of corn or soy oil in lowering plasma cholesterol is widely confirmed for adults (76 to 79) and for infants (80) When the vegetable oils were added to diets containing 25 gm. of butter, the effects were minimal (78); when 75 ml. of safflower oil was added to a diet with 100 gm. of animal fat, no fall in plasma cholesterol occurred (81), but as Kinsell points out, no fall should be expected when caloric intake is raised and large amounts of saturated fat are being ingested (82). While the effect of vegetable oils has been ascribed to their phytosterol content (83), removal of 80 per cent of the sterol (84) did not alter the effect, and adding corn oil sterols to other oils showed that this gave a small effect only (85). Although a rise in plasma cholesterol occurred in one study (79) when subjects switched from corn oil to fat-free diets, Horlick observed no fall in plasma lipide when patients' diets were changed from 4 per cent calories derived from fat to 25 per cent, from corn oil or ethyl lineolate, and no rise when shifted to ethyl stearate (86) A fall of 15 mg. per cent in plasma cholesterol within one hour after giving glucose by mouth was reported (87)

A diet with a protein content less than 25 gm /day lowered plasma and β-lipoprotein cholesterol even when there was 50 gm. of butter fat and 30 of vegetable oil in the daily ration Adding 1 gm of choline and 1 gm. of [illegible]

that these agents may raise plasma lipide when protein is severely restricted.

The cholesterol-lowering effect of sitosterols is generally confirmed (89). Added to a safflower supplement, the plasma level fell 60 per cent more than when either the oil or the plant sterol alone was given (90). Given intravenously, to animals, soybean sterol accelerated mobility of lipoprotein (91). No sitosterol could be found in either liver or the blood vessels after prolonged feeding to rats, rabbits, and dogs, using x-ray diffraction for detection (92). The cholesterol-lowering action of large doses (3 to 6 gms. a day) of nicotinic acid is confirmed (93, 94, 95). Nicotinamide has no effect (94, 95). The basal metabolic rate of patients taking 3 gm. of nicotinic acid daily rose by the end of a week, but the fall in cholesterol was great in relation to the rise in metabolism (96). In dogs, the fall is accelerated by doses of phenylethylacetic acid amide which, in themselves, have no effect (97). Alcohol extracts of brain tissue again were shown to lower plasma cholesterol, with 20 per cent fall if the level in patients was over 300 mg. per cent, 10 per cent when below 250 mg. (98). Retardation of atherosclerosis by exercise also has been stressed (99, 100).

A dietary factor much neglected recently, but carefully studied by Feigl in 1918, has been re-emphasized by Zieve (101). Acute alcoholism in well-nourished men produces very marked hyperlipemia and hypercholeterolemia, lasting for days Chronic alcoholism, with some impairment of nutrition and even hypoalbuminemia, may also cause hypercholesterolemia, rather than the low blood cholesterol of the advanced cirrhotic (101)

In rabbits, as in men, serum cholesterol fell on feeding safflower oil, rose on coconut oil (highly saturated), with changes in β-lipoprotein cholesterol much greater than in the lipoprotein nitrogen (102). In chicks, oleic acid caused higher serum, liver, and visceral cholesterol levels, but less aortic atherosclerosis, than did cottonseed oil (unsaturated) when given with 1 per cent cholesterol (103) In other rabbit experiments, the same serum cholesterol and aortic sclerosis resulted from diets with hydrogenated cottonseed oil, corn oil, or natural cottonseed oil, all at 35 per cent levels (104). In rats, plasma cholesterol was unchanged with hydrogenated and natural corn oil and safflower oil, with or without 2 per cent cholesterol, but liver cholesterol was higher in those given cholesterol plus unsaturated oils (105). When rats were fed cholic acid, cholesterol and tung, olive, safflower, coconut oils, or triolein, alone and in combinations to give a constant dietary fat level, the plasma cholesterol was highest on tung or olive oil or triolein supplement, lowest on half safflower and half coconut oil mixture. This led to the conclusion that lowering is related to the product of essential unsaturated fatty acid by saturated fatty acid, while nonessential (mono-ene) unsaturated fatty acids raise cholesterol levels (106). While there are anomalies, the rodent results are generally consistent with results in man, as summarized in Keyes (74, 75), on effects of polyunsaturated, monounsaturated, and saturated fats.

Pollak, confirming Altschul's observation that cooked cholesterol raised rabbits' plasma cholesterol more than did unheated material, found that hard

boiled egg added to rabbit chow raised blood levels tenfold, raw egg only threefold (107). A vitamin E-deficient diet raised rabbit cholesterol levels while administration of tocopherol caused a prompt fall (108). Rabbits fed cholesterol develop coronary insufficiency, revealed by electrocardiographic changes after injection of ergonovine. While 64 per cent gave positive tests on cholesterol alone, only 31 per cent were positive when 6 per cent corn oil was given with cholesterol. High plasma levels with negative tests, and relatively low cholesterol levels with positive tests were noted (109).

In cockerels, a high protein diet suppressed both hypercholesterolemia and atherosclerosis caused by cholesterol feeding The effect on the coronary vessels was notable with this diet In the aorta the effect was more striking if vitamins A and B were added; the vitamins alone had no effect. It was concluded that low methionine diets increased atherogenesis (110). In this species others (111) noted that the ratio of calories to protein in diet was significant, high protein levels reducing carcass and serum cholesterol whether corn oil or tallow was used as fat, but most strikingly with corn oil. When sucrose was substituted for protein in a high fat diet for cockerels, a drop of protein content from 20 to 10, or even to 16 per cent, led to aggravated hypercholesterolemia and atherogenesis occurred (112). In cockerels on cholesterol feeding, 20 mg. of heparin injected per day had no effect on plasma lipides or atheromas; it actually inhibited the effect of estrogen in reducing the plasma cholesterol and atherogenesis. Dicumarol also had no effect on plasma lipide or on aortic sclerosis and aggravated disease in coronary arteries (113).

Hypothyroidism also blocks the influence of estrogen in protecting the coronary arteries of cockerels fed cholesterol (114). Thiouracil is much used in cholesterol-high fat diets for production of atherosclerosis in rats. Careful comparison of effects of this agent in rats before and after ablating thyroid function with I^{131}, show that the drug must directly affect cholesterol metabolism, raising blood cholesterol in rats without any thyroid function (115). The lowering of hepatic cholesterol in rats treated with thiouracil is greater with tetraiodothyroformic acid than with thyroxine or tri-iodothyroacetic acid in doses having equal effect on O_2 uptake by the rat (116).

In the chick, estrogen protects only the cerebral and coronary arteries from atherosclerosis when cholesterol is fed; the lesions elsewhere are more severe on estrogen (117) In capons fed cholesterol, the least aortic sclerosis was seen in androgen-treated birds which had been exercised (118). Dogs fed diets with 40 per cent of calories from fat show only slight rise in blood cholesterol which, in females, is the same on lard or corn oil, in males the levels are lower on corn oil When given thiouracil, however, there is a marked rise in cholesterolemia when lard is substituted for corn oil (119). After adrenalectomy dogs show a drop in all plasma lipides and cholesterol feeding restores these with an average rise of 185 per cent in cholesterol, 330 per cent in lipide phosphorus, and 145 per cent in neutral fat Castration abolishes this response to cholesterol feeding (120)

The mechanisms by which unsaturated fatty acids, nicotinic acid, alcoholic brain extracts, and thyroid hormone and analogues reduce plasma cholesterol have been brought together and clarified by studies on absorption and excretion of cholesterol and bile acids which are derived from cholesterol. Using C^{14}-tagged cholesterol, it was shown that fatty acid is not needed for absorption of cholesterol into the enteric mucosa or into the lymph stream. Taurocholate is necessary, but dehydrocholate is ineffective in facilitating absorption of cholesterol (121). In normal men, thoracic duct lymph has half its cholesterol esterified (122) during absorption of C^{14}-labelled cholesterol, although previous studies showed that in the venous blood of normals most of the tagged cholesterol is not in the ester form in the first hours after absorption. These observations seem to show that esterified cholesterol entering via the lymphatic is rapidly de-esterified, and after entering the hepatic-plasma pool gradually becomes esterified again. In hypercholesterolemia, the ratio of esterified to free-labeled cholesterol is relatively high in the postabsorptive period (123).

When patients with hypercholesterolemia are put on diets rich in butter, there is a fall in the fecal excretion of sterols with C^{14} labels, after giving labeled cholesterol or labeled acetate which the body uses for cholesterol synthesis. On corn oil diets, the sterol excretion rises; Hellman and his coworkers found that sterol changes in total blood plasma almost exactly balanced the rise or fall in fecal excretion when the diet was altered (124) The alcoholic brain extracts (125), ascorbic acid (51), and thyroid hormone (126) also raise fecal sterol (including bile salt) excretion when lowering plasma cholesterol. In rats, corn oil produced a rate of fecal excretion of alpha sterols (nonprecipitable with digitonin) three to eight times greater than lard (127). In three patients with total external diversion of bile through fistulae, biliary excretion of cholesterol fell slightly and excretion of bile acid rose nearly threefold when dietary fat was changed from hydrogenated coconut oil to unsaturated sunflower seed oil Intravenous cottonseed oil emulsion raised the excretion of cholate fourfold, while lowering plasma cholesterol from 140 to 100 mg per cent (128).

While these studies leave no doubt as to how these oils, hormones, and vitamins rid the body of cholesterol, studies of rates of cholesterol synthesis, from C^{14}-labeled acetate, show that the liver increases its rate of formation of cholesterol not only with thyroid extract (129), but with corn oil diet (130), nicotinic acid (131), or phenyl-ethyl-propionate (132). The rate of degradation of cholesterol also is accelerated and serum levels reduced by [illegible] (133). [illegible] enough, cholesterol synthesis is [illegible] by total diversion of bile into [illegible] ed in pyridoxine-deficient animals (134).

The genetic factor in hypercholesterolemia was studied in 180 relatives and in 12 kinships, and it was concluded that the factors leading to xanthomatosis and coronary disease were transmitted as a simple Mendelian domi-

nant (135). A study by Schaefer, Adlersberg & Steinberg (136) dealt with a population of 1236, of which 775 were in 201 families. In the males, mean cholesterol values were constant from age 2 to 19, mean 178 mg. per cent; upper 5 per cent, 239 mg. per cent. Females were constant to age 32, with a mean 197 mg. per cent; upper 5 per cent, 256 mg. per cent. The main rise in males occurred to age 32, when the mean was 251 mg. per cent; upper 5 per cent, 318 mg. per cent. In females, the rise continued from 32 to 58 years, when the mean was 274 mg. per cent; upper 5 per cent, 350 mg per cent. The mean level for males of 32 years and older was reached by women only at age 45. The study of the families led to the conclusion that genetic factors were important in determining the level of blood cholesterol in a given environment, and that the transmission was not sex linked (136). A further study of serum cholesterol of 82 pairs of twins, living together and living apart, showed that the variance between values for a pair was least in monozygotic males living together, and was greatest in female dizygotes or twins of unlike sex living apart. Female monozygotes living apart had relatively large variances (137). While the effect of inheritance in establishing cholesterol plasma levels is demonstrably large, that of environment is also very great even when dealing with a population living in the same social strata of a single metropolis. The studies of Japanese in Japan, Hawaii, and Los Angeles (31) show how great are the effects of environment on members of one race in very different cultural surroundings and on different diets

The effects of sex, especially in relation to coronary disease, seemed to be very clear-cut two years ago. In chicks and in humans, the aorta showed similar degrees of atherosclerosis, but the coronary lesions were more severe in males Estrogens given to cockerels changed the ratios of cholesterol to phospholipide to that found in pullets, and prevented coronary sclerosis (138). In humans, estrogens lowered the ratio of β- to α-lipoprotein (139), and death rates from coronary disease were said to be low in men with prostatic cancer treated with estrogen (140). In those with healed infarction, death rates were much lower in one series of estrogen-treated cases as compared with controls (141), but no protective effect was apparent in the careful studies of Boyd & Oliver (142), although the serum cholesterol and the cholesterol/phospholipide ratio were reduced.

Keil and McVay report that deaths reach a peak earlier in life in negresses than in negroes and much earlier in negresses than in white women (143). Studies of the percentage of the aorta occupied by fatty streaks confirm this reversal of sex predisposition in the negro Holman and his colleagues reported that at eight years of age white boys and girls had 4 per cent of intimal lipoid streaks, negro children 6 per cent. At 18 years the values were 20 per cent for white males, 8 per cent for white females, 20 per cent for negro males, 24 per cent for negro females. The sex differences in whites gradually narrowed with aging after twenty, but were maintained in negroes up to age 45 (144). This reviewer has noted that studies of coronary intimal infiltration (145) by Lober showed a great spurt in white males, but none in white

females, between the ages of 10 and 30, and that dietary studies, in rural New York, Iowa, and several western states all show a very sharp rise in intake of animal fats by white boys between the ages of 10 and 16 years, with no rise and even a decline in intake by girls. No dietary surveys on negro adolescents are available, but it is now apparent that diet may play a large part in sex differences in atherosclerosis, and that the findings in the American negro are the reverse of those in whites, or in chickens.

Estrogen analogues are reported which cause changes in cholesterol levels in men (146) with minimal "feminizing" effects. Eunuchs show, as do women, low ratios of β- to α-lipoprotein, but only young castrates show lower blood cholesterol levels (147). When coronary patients are given estradiol 17 B (300 to 500 μg.), their excretion of estriol in relation to estrone rises much more than that seen in controls (148).

The effects of stress in elevating plasma cholesterol (149), together with acceleration of coagulation (150, 151), have been observed in following groups of subjects exposed to the usual "socio-economic" stresses. The stress of acute illness and hospitalization was found to cause little change in plasma cholesterol, but a marked increase in the fraction easily extracted by solvent, as well as a rise in unesterified fatty acid (152). A remarkable increase in atherosclerosis in most species of animals and birds (up to 40 times as severe as 40 years ago) is reported from the Philadelphia zoo. The diet was enriched in vitamines and fats over 20 years ago, but the most striking increase in vascular disease occurred only in the past decade, and is ascribed to crowding, inactivity, "social pressure and increased reproductive drive" (153).

Such effects of stress presumably are mediated through the hypothalamus and endocrine systems The thyroid hormones are mobilized during stress, but these hormones, and synthetic analogues with less effect on heat production (154, 155), all reduce plasma cholesterol Epinephrine, in long-acting suspension, causes a rise in triglyceride within one hour, in lipide phosphorus and cholesterol within a day (156). In rats, ACTH causes severe atherosclerosis in females, but none in males (157). In normal dogs, or adrenalectomized dogs given cortisone, the heparin antagonist, protamine, causes a rise in plasma lipides (up to 40 per cent increase), but it causes no rise in adrenalectomized animals not on cortisone (158). This suggests that stress may increase or potentiate heparin antagonists and affect both lipides and coagulation in that way.

Coronary attacks and hospitalization for such attacks deserve high place among stressing situations, and the level of lipoprotein lipase cofactor is lowest (or antagonist to heparin highest ?) at that time (58). Also at that time, corn oil has little or no effect in lowering plasma cholesterol, and in

an additional reason for use of heparin in therapy during these weeks.

Probably related to the stress or endocrine alterations in plasma lipide

is the rise in blood cholesterol in rats with hypertension, as compared with controls on similar diet and medication (160), and the fall in plasma cholesterol when patients have hypertension lowered by reserpine, reserpine and hydralazine, or ganglionic blocking agents. The fall parallels the change in pressure rather than drug or dosage of drugs (161, 162). Thus, the higher incidence of vascular accidents in hypertension is related not only to mechanical stress and to higher filtration pressure forcing lipides into the vessel wall, but to an elevation of plasma lipides evoked by the same factors which are acting to cause hypertension, or by hypertension itself.

The role of high pressure in causing rapid infiltration of vessel walls has been studied by Waters (163). When arterial pressure, in dogs, is maintained above 200 mm Hg for more than 30 min, some swelling and infiltration of the media is demonstrable in sections of the arteries. If alimentary hyperlipemia is present during the epinephrine infusion, histologically evident lipide accumulates in less than an hour, and persists for 2 to 3 weeks. If heparin is given prior to the injection no lipide appears in intima or media, but if given afterward the resolution is not hastened (163). Waters also observed the effects of allylamine which causes mild vascular damage, on the deposition of lipide in the coronary arteries (164). If normal dog's serum is dried, a clear solution is obtained on adding water. If the dog has induced hypercholesterolemia, the solution is turbid, since 10 to 15 per cent of the cholesterol is bound to protein denatured by drying. If the serum cholesterol is over 400 mg per cent, 30 per cent may be insoluble. Injection of the denatured material into the cornea causes persisting lipide-containing lesions while clear serum causes none. Intravenous injection of denatured lipoprotein causes similar lesions in coronary arteries injured by allylamine. Clear serum infusion after allylamine, or denatured serum without allylamine causes no such lesions of the coronary wall (164). Thus, the complementary roles of vascular injury and of altered serum lipides are clearly demonstrated. The relations between pre-β-lipoprotein, "easily extractable" cholesterol, and easily denatured lipoprotein need to be clarified, since all are said to be highly specific fractions related to atherogenesis.

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DISEASES OF THE CARDIOVASCULAR SYSTEM (SURGICAL)[1]

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This year completes the first decade of elective cardiac surgery and marks the quarter century point in Dr. Claude Beck's monumental work with coronary artery disease. The last anatomical frontiers of surgery have been pushed back. The infinitely more complicated chemical and physiological aspects are being challenged. Corrective or, at least, palliative surgery is now available for virtually every congenital or acquired defect in the cardiovascular system. It is obligatory for the physician to think of surgical intervention whenever the treatment of heart disease is involved.

MITRAL VALVE

Mitral Stenosis

Ten years have passed since the initial reports of successful surgical correction of mitral stenosis by Harken (1) and Bailey (2). During this first decade of modern elective cardiac surgery, the technique for the surgical correction of mitral stenosis by the closed method has been standardized and accepted For pure mitral stenosis, the closed technique is still advocated by Harken (3), Bailey (4), and Lillehei (5).

Bailey & Hirose (4) recommend the right-sided approach and have coined a new phrase "neostrophingic mobilization" for a method which, in their hands, has produced more acceptable results Two hundred twenty-seven patients have been operated by this method. Satisfactory mobilization of the mitral valve has been accomplished in 70 per cent, acceptable in 10 per cent, and unsatisfactory results obtained in 20 per cent Their surgical mortality rate seems high, i e., 8.6 per cent in 150 patients operated without maximal leaflet mobilization and 2 5 to 10 per cent since. Unfortunately, their results cannot be compared with other series because of lack of classification

Our first 1000 valvuloplasties for mitral stenosis (6) showed gratifying mortality reduction to less than 1 0 per cent for Group III patients. A mortality of the order of 20 per cent, however, still plagues the terminal or Group IV patients This again emphasizes the importance of operating in th[illegible]

sis, that is, below the leaflet level in the fused chordae, 10 years ago when the term valvuloplasty was introduced In more recent years, it has become

[1] The survey of literature pertaining to this review was completed in July, 1958.

obvious that more effective leaflet mobilization is obtained if the posteromedial commissure is opened as well as the fused anterior commissure. We have found the right-sided approach unsuited to good anterior commissural opening, difficult for safe clot evacuation and, of course, impossible for removing the auricular appendage. These important factors can be dealt with through the left-sided approach, if the surgeon is experienced and if he appropriately works first from the left then the right side of the table with the patient in the left lateral position. Under these conditions, closed mitral valvuloplasty seems preferable to commissurotomy, right-sided neostrophringic mobilization or open valvuloplasty. These are not mere words or technical considerations; they embrace the basic concepts and philosophy which control the quality of results.

Likoff & Urricchio (7) have analyzed 200 individuals surviving five to eight years after mitral surgery. Eighty per cent remain free of dyspnea, 90 per cent free of hemoptysis, and 50 per cent free of recurrent edema. This degree of response has been documented in our own series reported by Ellis, Abelmann & Harken (6), wherein 80 per cent of the Group III patients have been rehabilitated and 60 per cent of the Group IV patients have enjoyed similar improvement. To a remarkable degree, these results have been sustained through the years

Re-stenosis of the mitral valve is being recognized more frequently. Belcher (8) has reported 12 instances of "re-stenosis" in a series of 240 original operations. Eight of these were classified as being false re-stenosis. It is suggested that this is a function of inadequate original correction. Four patients are thought to have had true re-stenosis; this emphasizes the importance of adequacy of the initial operation. This result agrees substantially with our own experience. So-called re-stenosis has been traced to inadequate commissural opening and subleaflet mobilization at the first operation. This disappointment should be less common with experience. True re-stenosis associated with rheumatic activity, thrombus, etc., can occur, but it is rare. Iatrogenic or rheumatic regurgitation too often accounts for regression after operation. This type of mixed lesion is difficult to evaluate clinically and even by left heart catheterization.

D'Angelo, Murdaugh & Sealy (9) have studied the nature of the post-commissurotomy hyponatremic syndrome. Analysis of five patients revealed a concentrated low-volume urine output, low serum sodium and chloride with increased serum potassium and electrolyte dilution There was also decreased plasma osmolarity. Treatment by the administration of 20 to 50 cc. of absolute alcohol intravenously resulted in a diuresis with return of plasma osmolarity and electrolytes to normal levels Their studies suggest that this type of therapy causes a true water diuresis with conservation of sodium and potassium.

Embolization incident to mitral surgery still constitutes an intraoperative risk. This is of the order of 3 per cent in individuals in Group III who have previously embolized and as high as 9 per cent in Group IV in the same

category (3). Crane (10) has reported 14 patients with saddle embolus to the bifurcation of the aorta, 12 of whom had known mitral stenosis. There were 4 operative deaths; 2 survivors required subsequent amputation. Of the 10 surviving patients, 8 have undergone mitral valve surgery, 4 prior to and 4 subsequent to embolectomy. This type of complication should be recognized promptly in individuals with mitral stenosis, and surgical removal is often the treatment of choice

Kaufman & Ruble (11) have collected a large series of patients who have undergone cardiac surgery during pregnancy. Included are 93 patients with mitral valve disease. There have been three maternal deaths which occurred early in the experience of the various authors reported. These authors have noted that the hemodynamic changes in pregnancy usually become significant early in the second trimester. They recommend, in most instances, surgical intervention in preference to abortion although ideally, corrective cardiac surgery should be accomplished prior to pregnancy.

Our own series of 27 patients has been reported (12). There were three maternal deaths, and in only one was pregnancy a contributing factor. Corrective surgery should be performed before pregnancy. However, the patient with mitral stenosis may become pregnant, and the risk of cardiac surgery may be less than that of interruption of the pregnancy and subsequent valvuloplasty Previous cardiac surgery is not an indication of Caesarean section.

Proctor *et al.* (13) have examined the phonocardiogram in mitral valvular disease in 49 patients In individuals with mitral stenosis, the Q-1 time was prolonged on the average, but there was poor correlation with mitral valve size, left atrial mean pressure, and the end diastolic gradient across the mitral valve as determined at left heart catheterization The interval from second sound to opening snap correlated with the mean left atrial pressure, but this pressure and the gradient across the mitral valve could not be predicted on the basis of the measurement. They conclude that this is a useful ancillary tool but is not a substitute for adequate hemodynamic studies.

Wat & Barrie (14) have recognized long-standing thrombosis of the pulmonary artery as a serious complication of mitral stenosis. Three female patients subjected to mitral surgery died shortly thereafter and were found to have occlusion of one or more of the main branches of the pulmonary artery. Occlusion was more often on the right side. The mechanism was thought to be accretions of thrombus superimposed on pre-existing emboli They also reported six unoperated patients who died approximately 7 wk. after pulmonary thrombosis. They believe that angiocardiography is the best diagnostic method.

Mitral Insufficiency

Mitral insufficiency remains a most challenging problem. One limiting factor has been the difficulty of preparing a suitable experimental preparation for critical evaluation This may be, in part, solved by the work of

Kuykendall, Ellis & Grindlay (15). They have prepared animals with chronic mitral insufficiency by inserting a nerve hook into the left ventricle and drawing a suture around the chordae of the mural leaflet. Their results were reproducible with 75 per cent survival, and the animal's clinical course resembled that of humans with pure mitral regurgitation.

Rumel & Cutler (16) have treated mitral insufficiency with a wedge-shaped Ivalon prosthesis. Two tails extend from the apex and one from the base. This prosthesis is placed in a transvalvular position, with the two apical tails extending through the atrial wall and the basal tail through the ventricular wall. This has been tolerated in animals and patients with correction of the mitral regurgitation. Among their five patients, there are three survivors now living, five months later. There have been neither hemolytic nor thromboembolic phenomena. Probably this is a result of vascular fibrous tissue infiltration and surface endothelization.

Bakst *et al.* (17) have described an experimental closed technique for placing a four-tailed pericardial and muscle graft. Three of the tails are attached above the posterior margin of the mural leaflet by sutures passing through the ventricular wall and the tails of the prosthesis. The fourth tail passes through the orifice at the mitral valve and is anchored in the posterior papillary muscle and acts as a chorda for the prosthesis This has not been tried in human beings.

Davila and his associates (18) have now reported additional experience with their purse-string suture about the mitral annulus to correct insufficiency. Of 25 patients in intractable failure, 5 were found at operation to be unsuitable for this procedure Three are living of the remaining 20. Twenty-three patients in chronic but not intractable failure have been operated upon with 5 operative deaths and 2 late deaths, 16 survivors. They suggest that these operations must be performed earlier in the course of the disease and in the presence of adequate valvular area, mobility, and flexibility. Myocardial exhaustion and complete valvular damage preclude successful correction The authors of this review abandoned this operation over two years ago.

Lillehei *et al.* (5) describe an open operation for mitral insufficiency using extracorporeal circulation. Their reported experience is not large, but their results have been encouraging Two techniques have been used: one is selective suturing of the annulus in the posterior commissure under direct vision; the second is the use of an Ivalon and silastic prosthesis which supplements the mural leaflet. Their approach is through the right chest with posterior left atriotomy.

Scott, Daniel & Schull (19), utilizing by-pass technique, have approached the left atrium through a left thoracotomy and arrested the heart with potassium citrate. They have sutured the annulus posteriorly with inter-

one patient died three months after surgery from a large atrial thrombus. Two had satisfactory results.

Kay & Nagueira (20) have accomplished open correction of mitral disease in 11 patients. Three had stenosis; eight, insufficiency. Both left- and right-sided approaches have been used. They now prefer the right. There was one death, the first in the series.

Mild to moderate amounts of mitral insufficiency are well tolerated in those individuals undergoing effective surgery for dominant mitral stenosis (6). Furthermore, these minor degrees of mitral regurgitation can be appreciably reduced by extrinsic baffles We have used this technique for more than two years (3). It consists of the placement of a rolled cylinder of compressed Gelfoam behind the dilated left atrium and above the annulus. Thus placed, it corrects valvular herniation with its attendant shortening of the chordae and relative loss of leaflet substance. Unhappy experience with intrinsic plastic prosthesis (21, 22) for severe mitral regurgitation makes us view some of the above suggestions with hope but concern. We are greatly encouraged by our initial experience with direct open operation for mitral insufficiency. As suggested by Wilson (23), we have explored the mitral valve by right atriotomy and incision of the interatrial septum. This affords direct exposure of the mitral vavle. Direct suture correction is accomplished while circulation is sustained with a pump oxygenator.

AORTIC VALVE

Aortic Stenosis

There is agreement on the desperate seriousness of aortic stenosis once the patient has congestive failure. Dyspnea, even mild, or overt failure are more ominous than angina or syncope. Bergeron *et al* (24) have clarified these prognostic signs and symptoms and accord atrial fibrillation seriousness equal to congestive failure.

Attitudes toward surgery vary from therapeutic nihilism, generally based on limited, unhappy, or insufficient surgical experience, to excessive advocacy of early operation by open technique. Review of the available experience with various techniques, and our own experience with all existing types of surgical correction of aortic stenosis, may justify optimism and clarify the time and place for various methods. A rational combination of the advantages of closed transaortic and open operation with pump-oxygenated by-pass seems best. This somewhat complicated picture can best be understood by reviewing various policies

Open aortic surgery by cardiopulmonary by-pass is advocated by Lillehei (5), who combines extracorporeal circulation and coronary sinus perfusion with a cardioplegic agent (acetylcholine) as needed. Spencer, Neill & Bahnson (25) also advocate open approach to aortic stenosis. Using cardiopulmonary by-pass, they have operated on 12 individuals with congenital aortic stenosis All patients survived with a significant reduction in the

gradient across the aortic valve in those having valvular stenosis. Reduction of the gradient was noted to a much less degree in four patients who had subvalvular stenosis. They emphasize again the danger of producing aortic insufficiency and the necessity for precise incision within the commissures, leaving thickened fibrous bands supporting each cusp. Swan, Wilkinson & Blount (26) have operated on aortic stenosis under direct vision using hypothermia, as did Lewis (27). Their report includes 8 with valvular stenosis and 3 with subvalvular stenosis. Eight of 11 patients survived; 4 had slight to moderate aortic insufficiency.

Gadboys, Harrison & Litwak (28) have developed an ingenious instrument with a fenestrated and nonfenestrated blade which can be introduced through a pericardial pouch. This instrument permits open exposure of the noncoronary cusp without inflow occlusion, by-pass, or hypothermia.

The closed approach to aortic stenosis can be subdivided into transventricular and transaortic. Glover (29) advocates transventricular fracture dilatation of the aortic valve. In a recent experience with 50 patients so treated, there has been an operative mortality of 6 per cent. Brock (30) also prefers the transventricular approach. In an earlier communication, he reported 76 patients with pure aortic stenosis operated by this technique with 12 operative deaths (16 per cent). An additional 34 patients, with combined mitral and aortic disease, had both lesions corrected, with three deaths occurring (9 per cent).

Our own attitudes with regard to this problem involve both open and closed technique (31, 32). Noncalcific aortic stenosis, be it congenital or acquired, valvular or subvalvular and in children or adults, is, because of its flexibility, often not amenable to closed aortic fracture dilatation. At the same time the noncalcific fusion zones adapt well to meticulous incision at open operation. Conversely in calcific aortic stenosis finger fracture is better than incision as attested by the overall operative mortality of 12 per cent. (In the last 60 patients, this was reduced to 8 per cent.) Our technique involves digital or instrumental fracture of the aortic commissures, or both, through an Ivalon operating tunnel sewn to the ascending aorta just above the valve. This eliminates extracorporeal circulation and is not limited by the time factor of hypothermia. Of 72 survivors, 50 have been followed 6 mo. or more. A substantial improvement has been noted in 86 per cent of these survivors.

Smith, Bailey & Goldberg (33) have presented pre- and postoperative data on 14 patients with aortic stenosis who have undergone simultaneous left and right heart catheterization. They demonstrated a failure of restoration of the altered physiology postoperatively. It is postulated that this is

[4] Our own pre- and postoperative catheterization results have shown significant *increases* in the aortic valve area, reduction in the gradient across

the aortic valve, and a reduction in the amount of left ventricular work (32, 34). A critical cross-sectional area of the aortic valve exists (0 6 sq. cm. or less). An operative procedure which corrects this severe stenosis, even though it fails to restore a normal valve ortifice, can be rewarded by substantial clinical improvement.

A word of warning has been sounded by Hancock *et al.* (35) with regard to aortic stenosis which seems typical by clinical examination but is shown at left heart catheterization to be of no significance. A careful analysis of seven patients who presented many of the clinical stigmata of aortic stenosis showed coronary artery disease in five instances; in two instances, mitral valve disease was present which had not been clinically suspected.

In summary, one can suspect that eventually aortic stenosis will be corrected by open surgery and valve replacement, but now the judicious use of the closed transaortic approach in calcific disease and open operation in noncalcific or subvalular stenosis seem best. When in doubt about the calcific nature of a valve and its suitability for the closed transaortic tunnel operation, the pump oxygenator may be held ready for open operation.

Aortic Insufficiency

The surgical treatment for aortic insufficiency is not as satisfactory as that for aortic stenosis Among the limiting factors has been the absence of a tool to assess the degree of aortic regurgitation present. Braunwald & Morrow (36) have reported retrograde aortic catheterization from the femoral artery, with determination of the lowest point in the descending aorta from which injected dye regurgitated back to the ascending aorta and perfused the carotid vessels. Sampling was performed by an oximeter placed on the right ear. In seven patients without aortic insufficiency, no dye reached the right ear until the perfusate was injected in close proximity to the carotid vessels. In ten patients with aortic insufficiency, dye was readily detected by the oximeter. A method of grossly partitioning the aorta has permitted some qualitative estimate as to the amount of regurgitation

Late complications, such as reported by Kittle (37), following insertion of the Hufnagel ball valve in the descending aorta have lessened the enthusiasm for this type of prosthesis. A false aneurysm surrounding the valve subsequently perforated into the esophagus 22 months after insertion. The author has analyzed an additional 10 cases done with 50 per cent overall mortality. We abandoned this operation over two years ago We had no technical difficulty in 12 patients, but the diastolic perfusion of coronary arteries seemed to be reduced The results were poor.

Garamella, Andersen & Oropeza (38), working in the experimental laboratory, have achieved correction of aortic insufficiency by a posterolateral incision in the aorta exposing and excising the noncoronary cusp. The defect in the aortic wall is closed, approximating the right and left coronary bearing cusps posteriorly, thus making a bicuspid valve. This procedure, which is

done while the animal is supported by extracorporeal circulation, has not yet had clinical application.

In selected instances of aortic insufficiency associated with a markedly dilated annulus, there is a place for annulus reduction by a circumcluding tapered silk suture such as Taylor *et al.* have reported (39). This technique is not applicable in the presence of heavy calcification but seems ideally suited in instances of syphilitic and noncalcific aortic insufficiency.

Hufnagel, Villegas & Nahas (40) have recently reported various modifications of the conventional ball valve, as well as other prosthetic approaches to aortic valvular disease The original ball valve has been modified. A silastic sphere incased in a plexiglass housing replaces the all plastic valve. The aorta is wrapped with a semielastic orlon mesh which "snugs" the host aorta to the intravascular portion of the prosthesis and eliminates thrombus formation at this juncture. In instances where aortic cross clamping is contraindicated, two methods have been advocated. First, a by-pass has been created from the subclavian artery to the distal aorta while the prosthetic valve is inserted. Secondly, they have accomplished end-to-side anastomosis of the standard prosthesis armed with a dacron or dacron teflon tubing. The interposed aorta is subsequently resected. Hufnagel has recognized that placement of the valve in the descending aorta accomplishes only 70 per cent reduction of reflux and is therefore attempting anatomic placement of artificial valves. One method is a conventional ball valve, in a fenestrated housing, secured below the level of the coronaries with a broad band of cloth and distally attached to the aorta by multiple-point fixation A second type is a tricuspid leaflet made of spring steel with silicone rubber cusps, which is also placed in the subcoronary portion This type of prosthesis has been used in dogs for periods up to six months without embolization or failure to function. A third type of valve is a helix spring type of prosthesis made of spring steel coated with teflon A proximal ring is placed beneath the coronary origins and held in this position by a circumcluding ligature Three vertical guide posts prevent the aortic wall from collapsing against the valve. These are held distally to the aortic wall either by sutures or by multiple-point fixation. A fourth method applicable when there is annulus dilatation involves excision of an excluded segment of aorta adjacent to the noncoronary cusps with subsequent reanastomosis of the incised edges.

In summary—The so-called standard methods of treating aortic regurgitation are less than satisfactory. Current laboratory and clinical efforts are extremely promising and are directed both at improvement of existing methods and their modification to include partial or complete prostheses in the normal valve location

LEFT HEART CATHETERIZATION

Catheterization of the left side of the heart is being used more frequently as surgery of aortic and mitral valves is expanded. Pressure gradients per

se are inadequate in hemodynamic appraisal Techniques are also needed for differentiating aortic and mitral insufficiency. Many groups are concerned with these limitations and are trying to solve the problems

Braunwald, Tanenbaum & Morrow (41) as well as Warner & Toronto (42) have independently approached the problem of evaluating aortic regurgitation by injecting an indicator (Evans Blue) into the descending aorta and sampling peripherally. Normally, without regurgitation there is a sharp upswing with a smooth downward slope of the resultant dye curve. In the presence of regurgitation, there is disruption of the descending limb of the curve caused by dye which may have regurgitated into the left ventricle. These men have also used this technique to localize shunts in the atrium or ventricle, where a recirculation of the shunted dye in the pulmonary circulation appears again on the down swing of the major dye curve.

Fleming *et al* (43) report 158 direct left heart catheterizations by left ventricular puncture, utilizing the original technique described by Brock, Milstein & Ross (44) They use a #16 needle through which a nylon or polyethylene catheter is advanced along the aortic outflow tract across the aortic valve. This technique has afforded excellent evaluation. There have been two deaths from hemopericardium. This emphasizes the danger of this diagnostic tool Yu and associates (45) have reported 30 patients subjected to direct left ventricular puncture (Brock technique) all without complication and with adequate data obtained. Greene *et al.* (46) have combined direct left ventricular puncture with the technique of left atrial puncture approached through the suprasternal notch (Radner) This method, combined with peripheral tracings, permits simultaneous assessment of gradients and flows across mitral and aortic valves. They have used this technique in 23 patients without fatality.

Tanenbaum, Braunwald & Morrow (47) are now using a technique of left heart catheterization at the operating table with simultaneous determinations of pressure gradient across the involved valve and central Evans Blue injection with peripheral sampling Inspection of the resultant dye curve immediately affords useful data on flow and insufficiency Subsequent analyses provide a more precise evaluation.

The authors of this review have used direct ventricular puncture, retrograde aortic catheterization, transbronchial puncture, and variations of the Bjork methods; the Fisher technique provides safety and dependability The intraoperative flow studies will be tried with interest

PULMONIC VALVE

Two basic concepts with regard to obstruction of the pulmonary outflow tract seem to be undergoing considerable change. The first has to do with the fact that surgically created pulmonic insufficiency is innocuous

Fowler & Duchesne (48) produced pulmonary insufficiency in 18 dogs. Eight survived and none had clinical evidence of limitation, but catheteriza-

tion studies one or more years later showed right ventricular dilatation and evidence of decreased cardiac output in all. This work would suggest that pulmonary insufficiency is not innocuous.

The second concept has to do with the adequacy of closed techniques for the correction of outflow obstruction. McGoon & Kirklin (49) have studied pulmonic stenosis with an intact ventricular septum. They have observed that "pulmonic stenosis without an IVSD" may be valvular, infundibular, or both and associated with an unsuspected atrial septal defect or previously unrecognized small IVSD (interventricular septal defect). It is their recommendation that this condition be approached always with open heart technique and extracorporeal circulation in order to correct all lesions. Ten patients have been operated on without mortality. An interatrial septal defect was encountered in 50 per cent, and in a larger series not individually reported, coexistent infundibular stensosis and valvular stenosis occurred in approximately 25 per cent.

Ehrenhaft *et al.* (50) also recommend open correction of pulmonic stenosis. In reporting 12 cases, they record no deaths. Eleven were corrected under hypothermia, one with a pump-oxygenator. Interatrial septal defect was present in 25 per cent of their cases.

Our own experience suggests that open correction is the most satisfactory method of approaching this problem. Either hypothermia or extracorporeal circulation seems satisfactory, although the latter provides a longer period of time for meticulous reconstruction of the pulmonic valve or resection of the infundibular stenosis. Ventricular hypertrophy with exaggeration of pulmonic outflow tract obstruction has proved to be a very real entity. The excellent correction of valvular stenosis, possible with open techniques, increases the hazards of major outflow tract hypertrophy. The surgeon must be mindful of these hemodynamic problems

Lundberg (51), and Engle and his associates (52) have stressed the importance of assessing the hemodynamic results following correction of pulmonic stenosis at a late date. Often, right ventricular pressures will remain elevated immediately after surgical correction of either valvular or infundibular stenosis; however, when assessed one to many months postoperatively the ventricular pressures will have returned to normal limits. There is often accompanying EKG evidence to suggest that the right ventricular hypertrophy has disappeared The obstruction in such instances is thought to be on the basis of marked muscular hypertrophy of the right ventricular outflow tract. Engle has suggested that if there is no fixed or fibrotic subvalvular stenosis found, no attempt should be made to resect muscle

Glenn and his associates (53, 54) have by-passed the right heart experimentally. Varying amounts of venous blood have been shunted from the caval system into the right pulmonary artery. The most successful results in animals were obtained when the superior vena cava was anastomosed end-to-side with the right pulmonary artery. The pressure gradient between the vena cava and the pulmonary artery was found to be sufficient to permit

adequate flow through the right lung. Approximately 30 to 40 per cent of the cardiac output was therefore by-passed around the right heart, thus reducing right ventricular work. This experimental success led them to the use of this technique on a seven-year-old child with a single ventricle, transposition of the great vessels, and pulmonic stenosis. The right pulmonary artery was divided, and end-to-side anastomosis with the superior vena cava was accomplished. The cava was ligated between the anastomosis and the right atrium. There has been marked clinical improvement in a cyanotic and limited child. Glenn believes that this type of shunt may be useful in right sided anomalies not suitable for open heart surgical correction. A similar experience has been reported by Robicsek *et al.* (55). These authors have observed no significant increase in superior vena caval pressure. Blood flow and oxygen uptake in the right lung are comparable to that observed on the left side. There has been no alteration in the main pulmonary artery pressure.

TRICUSPID VALVE

Mayer, Nadas & Ongley (56) have recorded 10 instances of Ebstein's anomaly (malformation of the tricuspid valve, atrialization of the ventricle, and associated atrial septal defect). The patients are usually mildly symptomatic with cyanosis, dyspnea, fatigability, and bouts of palpitation. Physical findings include evidence of normal growth, frequent cyanosis, infrequent clubbing, and a quiet cardiac impulse with a systolic thrill between the xiphoid and apex A triple or quadruple rhythm is often noted, and there is a diminished pulmonic second sound. Systolic and diastolic murmurs at the lower left sternal border and the apex are frequently observed. Phonocardiograms show a delayed first sound, a systolic murmur, and a presystolic murmur, with a less constant mid-diastolic murmur at the apex.

Characteristically, the electrocardiogram shows tall P waves, prolonged atrioventricular conduction, and right bundle branch block with low potentials over the right ventricle. X-rays demonstrate cardiomegaly, right-sided enlargement with a narrow base There is a diminution in the pulmonary vascular markings and a poorly delineated pulmonary artery. Angiocardiography demonstrates a huge right atrium with delayed emptying and frequent evidence of a right-to-left shunt. Catheterization of the right side of the heart likewise documents the large atrium and displacement of the tricuspid valve to the left. There is moderately elevated right atrial pressure, normal right ventricular systolic pressure, and an absence of a gradient across the pulmonary valve Peripheral arterial oxygen unsaturation is frequently observed.

Tricuspid valvular insufficiency has been evaluated by Musser *et al* (57). Radiopaque material is injected directly into the right ventricle, and a positive result is determined by evidence of the dye substance in the right atrium. In dogs with normal tricuspid valves, no regurgitation has occurred into the atrium; and the same has been observed in three patients with

aortic stenosis and normal tricuspid valves. Additional experience with 11 human beings has shown a good correlation with the clinical, surgical, and autopsy findings.

While these studies are of great value in increasing our knowledge of the functional and hemodynamic aspects of tricuspid disease, this particular valve has rarely presented critical clinical problems. Tricuspid stenosis is infrequently found and, when encountered, is associated with mitral stenosis. When this condition is suspected, digital exploration of the right atrium and correction of existing stenosis are readily accomplished at the time of mitral valve surgery. More often, relative tricuspid insufficiency exists, and exploration will reveal a patulous opening caused by dilatation of the annulus. Adequate correction of the underlying mitral disease successfully corrects the hemodynamic defect (3), and the relative tricuspid insufficiency or stenosis (58) ceases to be significant.

EXTRACORPOREAL CIRCULATION

The rapid expansion of work with extracorporeal circulation brought about a timely conference among the leading workers throughout the world. This important meeting was a work conference sponsored by the Surgical Study Section of the United States Public Health Service. The symposium was held in Chicago, September, 1957 and proceedings are available in monograph form (59) The magnitude, diversity, and minute detail of material renders abstracting here undesirable. Not only was a great deal of information exchanged by key groups, but so also was standardization of technique and terminology which should be of lasting benefit.

At the present time, bubble, disc, standing screen, and membrane oxygenators are being used. There has been considerable concern over the infusion of microscopic air bubbles or other noxious elements from bubble types. Poor experimental and clinical experience has led many groups to abandon this oxygenator. The facts remain, however, that those who have had the greatest experience with this type of machine have achieved excellent clinical results.

The recent literature has not brought forth fundamental modifications of the screen, disc, or membrane oxygenators However, a number of variations of the standard bubble oxygenator have been described. Gott *et al* (60) have described a disposable unitized plastic sheet oxygenator. This is a two-dimensional modification of the original DeWall apparatus. In their experience it has functioned as well as its three-dimensional prototype. The same values for oxygenation, acid base shift, and hemolysis have been observed. The apparatus is presterilized Clinical experience has included success in 11 patients Cooley and his co-workers (61) have developed a stainless steel bubble-type oxygenator composed of a diffusion plate, oxygen column with an open inclined trough, defoaming chamber and reservoir. This type of equipment, used in conjunction with a Sigma-motor pump, has had extensive successful clinical application Merendino *et al.* (62) are using

a plastic oxygenator in which a baffled collecting chamber is superimposed on a lower bubbling chamber. This apparatus has produced 98 per cent saturation of arterial blood with flows varying from 200 to 4000 cc. Milnes *et al.* (63) have also developed a plastic oxygenator which has a central bubbling tube and an outer concentric collecting chamber. They have avoided air emboli by the use of a deep blood reservoir. Static foam and fibrin emboli have been eliminated by placing a plastic mesh over the oxygenating column Extensive experimental use of this device has convinced these authors that perfusion with flow rates of 75 cc. per kg. may be employed without danger of air emboli.

Panico (64), while working in our laboratory, developed a concentric oxygenator which had experimental and clinical application. We have now abandoned this and other bubble type oxygenators in favor of a modification of the Gross and Kay-Cross disc oxygenator which is giving complete satisfaction for operations of 1 to 1½ hr.

Tissue, metabolic, and hematologic alterations.—Many reports have dealt with tissue, metabolic and hematologic alterations incident to exteriorizing a large proportion of an individual's blood volume. Andersen & Senning (65) carried out animal experiments in order to relate flow rate to oxygen consumption. In dogs perfused at 20 to 30 cc. per kg. per min., oxygen consumption was reduced to 50 per cent of the control value. As the flow rate was increased, oxygen consumption rose to the control levels with 100 cc. per kg. per min. The decline in oxygen consumption at the lower rates appeared to result primarily from decreased circulation rather than from a fall in arterial blood pressure Artificial elevation of the blood pressure produced a slight increase in oxygen utilization but not to control levels. The authors conclude that maintenance of flow rate is important, even though arterial saturation may be below optimal levels

Clowes and associates (66) studied the relationship of oxygen consumption, perfusion rate, and temperature to the development of acidosis during circulatory by-pass. In those animals with a high flow rate, i.e., in excess of 70 cc per kg., there was 85 per cent oxygen consumption as opposed to 47 per cent in the low-flow group. Acidosis and lactic acid accumulation were inversely proportional to the perfusion rate despite maintenance of normal arterial CO_2 tension. In a group of animals subjected to hypothermia at 30° C., oxygen consumption was 75 per cent of the comparable normothermic animals Lactic acid accumulation and fall of pH was less pronounced in this group.

Sturtz *et al.* (67, 68) have determined alterations in the water metabolism in 21 postoperative patients who had undergone cardiac operations using a Gibbon type oxygenator Body weight decreased daily on the average of 200 to 400 gm per sq m. Serum water was low after perfusion but returned to normal in 7 to 10 hr Insensible water loss averaged approximately 400 ml. per day and urinary output which was mostly obligatory was of the order of 300, 450 and 500 ml. per sq. m. on the first, second, and third post-

operative days. The authors recommend that fluid requirements for the first day should be 500 cc. and 750 cc. on the second and third days Their data further suggest that the insensible water loss which is strikingly increased during open cardiac surgery is largely an effect of exposure of pleural and pericardial surfaces and is not related to the apparatus used.

Andersen, Norberg & Senning (69) have evaluated liver function during extracorporeal circulation at low flow rates (29 to 63 cc. per kg.). There is a marked transient rise in portal pressure with a less pronounced elevation of pressure in the inferior vena cava. Hepatic metabolism of lactic acid is essentially normal, and there is no unusual liberation of potassium from the liver or elevation in systemic potassium levels. Sulfobromophthalein excretion was depressed during and immediately after by-pass, but shortly returned to normal.

The most extensive study of physiologic response to total body perfusion has been reported by DeWall and colleagues (70). One hundred twenty patients undergoing open cardiac surgery were evaluated. There was no significant alteration in the pH. In 31 cyanotic patients, the control pH was within acidotic levels but this was not increased during perfusion. In those individuals in whom the underlying defect was successfully repaired, there was a return to normal levels of pH within 18 hr Depression of the plasma bicarbonate occurred in all patients, but it was less marked in the cyanotic group. The depression was roughly the same as seen in other surgical patients. Serum potassium levels declined during perfusion, and this was more marked immediately postoperatively, with return to normal limits within 2 hr. The authors postulate that this is related to a rise in glucose which is both endogenous as a result of adrenal response and exogenous as a result of infusion.

Ferbers & Kirklin (71) carried out studies on hemolysis with a plastic sheet bubble oxygenator originally described by the University of Minnesota group (60). Three thousand cc. of fresh blood were circulated at 550 cc. per min. with a 2 L. oxygen flow. Three hundred fifty mg per cent hemolysis occurred at the end of 1 hr., and 500 mg. per cent at the end of 2 hr. When this same oxygenator was used with an animal in the circuit, the hemolysis did not rise above 30 mg. per cent at the end of 1 hr. Presumably, the free hemolyzed material was picked up by the reticuloendothelial system and eliminated as bile pigments. In commenting upon the danger of hemoglobinemia, Ferbers and Kirklin note that this condition will produce chills, fever, cramps, and vomiting. It will also contribute to peripheral dilatation, hypotension, bradycardia, and impaired cardiac output It is their thesis that the marked hemolysis is occasioned by turbulence created by oxygen jets.

Baffle & Hewlett (72) carried out blood studies on 12 patients following open heart operations with a rotating disc oxygenator. These oxygenators were of the Bjork, Kay-Cross, and Melrose types. Their observations demonstrated a mild anemia, minimal hemolysis, leucocytosis up to 23,000 per

c. mm., the presence of atypical lymphocytes, and slight reticulocytosis There was a minimal prolongation of the prothrombin time.

Continual monitoring of cerebral activity during extracorporeal circulation with an electroencephalogram has been advocated by the groups at the University of Minnesota and the Mayo Clinic, and by Vandam of the Peter Bent Brigham Hospital Owens and his associates (73) have made EEG observations during by-pass in 150 dogs and in 23 patients. Various oxygenators were used. The results demonstrated undesirable alterations in all instances when a bubble oxygenator was employed; however, with filming oxygenators little deviation from the baseline was observed. This is consistent with the experience of the authors of this review and has contributed to the changes mentioned previously.

Pulmonary complications of open heart operations are the subject of a report by Kolff and his associates (74). These authors conclude that temporary overloading of the pulmonary circuit with blood is the most important single factor in initiating capillary damage and the early phases of severe pulmonary complications. Four mechanisms of overloading are suggested: (*a*) forward overfilling of the pulmonary vascular bed, such as may occur during partial by-pass with an expanded blood volume prior to the establishment of the total by-pass; (*b*) filling of the pulmonary vascular bed through collaterals, (*c*) retrograde filling of the pulmonary vascular bed from the left side of the heart either as a result of impeded venous outflow through the pulmonary veins or of backflow from a hypertensive left heart; (*d*) a combination of the above. Avoidance of temporary overloading of the pulmonary circulation is advocated This involves reduced right heart burden and left atrial decompression during surgery.

The danger of trapping air within a chamber of the heart following open cardiotomy is ever present. While this complication is infrequent, it can be fatal if unrecognized. Various prophylactic methods include filling the chamber with saline, Ringer's solution, or with blood either antegrade or retrograde. Nichols, Morse & Hirose (75) have also noted that air within the chambers may be displaced by carbon dioxide that will, in turn, be rapidly dissolved in blood.

Open intracardiac surgery has been extended by induced cardiac arrest. The potassium citrate technique of Melrose (76) has been used extensively. However, many have noted a disturbing incidence of refractory ventricular fibrillation following re-establishment of coronary circulation This is typified by the experience of Kaplan *et al.* (77) in which survival following total by-pass and potassium arrest in dogs was 50 per cent as opposed to 90 per cent in animals where the heart was not arrested Lam (78) has advocated the use of acetylcholine as a cardioplegic agent with considerable success. This agent, however, has the disadvantage of not achieving complete clinical and electrical standstill The quest has persisted for a more acceptable and effective agent or combination of agents.

Milnes and associates (79) induced asystole with a mixture of potassium

citrate and magnesium sulphate buffered with sodium bicarbonate. Consistent survival was obtained in laboratory animals, provided the period of asystole was limited to 35 min. or less. Sealy *et al.* (80, 81) have used a combination of potassium citrate, magnesium sulphate, and neostigmine. Work in normothermic and hypothermic animals has suggested that potassium and magnesium are synergistic and more efficient in combination than when used alone. Cooley (82) has recently abandoned potassium arrest and is relying on intermittent aortic occlusion to afford visualization within the cardiac chambers. Anoxic cardiac arrest frequency occurs with this type of occlusion. This type of arrest is adequately tolerated by the myocardium Crafoord (83) has also used anoxic arrest with success.

HYPOTHERMIA

There has been a dramatic shift away from hypothermia in cardiac surgery. The high incidence of ventricular fibrillation during inflow occlusion in an hypothermic individual has long been recognized as one of the chief limitations of this technique. Current investigation is largely directed toward methods of avoiding this complication. Caranna, Telmosse & Swan (84) have noted a marked degree of protection against ventricular fibrillation in dogs which have been perfused intravenously with various nutrient solutions. They postulate that these nutrients provide glycogen, which is stored in the myocardial tissue and later used during the anoxic period. Berman, Taylor & Fisk (85) have induced cardiac arrest in hypothermic dogs with a mixture of acetylcholine and quinidine In animals so treated, there has been a significant decrease in the incidence of ventricular fibrillation, as opposed to their experience with other agents Ribera & Shumacker (86) have also tested various agents for production of elective cardiac arrest under hypothermia The most effective agent, in their experience, has been sodium lactate to accomplish clinical and electrical standstill. Restoration is brought about by perfusion of the coronary arteries with oxygenated blood until good color has been restored, followed by perfusion with calcium gluconate. Brockman & Fonkalsrud (87) have used methacholine bromide (Mecholyl) arrest combined with carotid perfusion by oxygenated blood. In a control series, they found inflow occlusion could not exceed 20 min. unless accompanied by carotid perfusion However, 20 dogs were cooled to between 27.5 and 30° C Circulatory arrest was accomplished for 32 to 50 min, with carotid perfusion at the rate of 1.3 to 3 6 cc per kg. These dogs survived, with the exception of one that subsequently died from an empyema. One dog with a very low perfusion rate demonstrated ataxia but, otherwise, there were no neurologic sequelae. Methods such as these may well extend the time for inflow occlusion and, thereby, further enhance the use of hypothermia in open heart surgery.

Sealy, Brown & Young (88) have also recognized the time limitation in hypothermia for open heart surgery, and, accordingly, have combined cooling with extracorporeal circulation. Forty-nine patients have been operated

on at temperatures ranging between 28.5 and 32° C. while their circulation was supported with a modified DeWall oxygenator. Perfusion rates have been low in the range between 20 and 50 cc. per kg. per min. Despite this low flow rate, there have been consistently high levels of venous oxygen saturation, and systolic blood pressures have been maintained in the range of 40 to 90 mm. Hg, averaging about 50. There have been only minor alterations in the lactic acid level. In the last nine patients, they have used the Brown-Emmons heat exchanger which has permitted rapid cooling and rewarming within 10 to 15 min. of partial by-pass Twenty-four of 25 patients with interatrial defects and valvular stenosis have survived, and 12 of 21 individuals have lived who were subjected to ventriculotomy.

INTRACARDIAC SEPTAL DEFECTS

Atrial Septal Defects

Much current literature dealing with interatrial septal defects has to do with experience with and results obtained by using extracorporeal circulation. There are, however, many advocates of various closed techniques and open correction under hypothermia.

Hirose, Morse & Bailey (89) have currently modified their technique of atrioseptopexy. A finger inserted into the left atrium through the interatrial groove palpates the defect from the left side. The interatrial finger guides sutures placed to obliterate the defect by invagination of the right atrial wall. Cooley, *et al.* (82) advocate open correction of interatrial septal defects, utilizing their modification of the bubble oxygenator (61). Their initial series of 27 interatrial septal defects using this technique resulted in 25 successful closures and 2 deaths.

Lewis (90) has considered the problem of the high interatrial septal defects so often associated with aberrant venous drainage Surgical correction is often complicated by pulmonary venous or superior vena caval thrombosis. The danger lies in too great constriction of the site of entry of the superior vena cava or of the pulmonary veins He suggests refraining from transposing all of the aberrant pulmonary venous drainage, or the use of an Ivalon prosthesis.

The authors of this review have abandoned closed techniques and hypothermia for interatrial septal defects in favor of open surgery using a disc oxygenator. The uncertainty of diagnosis makes by-pass availability a necessity. The importance of careful, deliberate, and meticulous intracardiac work precludes hypothermia.

Interventricular Septal Defects

Brotmacher & Campbell (91) have analyzed 75 proven cases of interventricular septal defects (IVSD) in patients who have had right heart catheterization Their analysis has traced the natural history of such defects. Seventy-five per cent of the individuals were less than 20 years of age.

Equal sex incidence occurs under 20, but more females survive after age 20. If individuals with ventricular septal defects survive infancy, they apparently have a good prognosis for 15 years with deterioration occurring thereafter. There are few surviving beyond the age of 40. Pulmonary artery resistance increases with age, associated with subsequent rise in the right ventricular pressure and increased right-to-left shunt.

Kirklin & McGoon (92) have described in detail the anatomy of high ventricular septal defects. The technical considerations involved in closing such defects, which may be just below the pulmonary and aortic valves, are outlined. The importance of thorough knowledge of the anatomy is stressed. Their experience as well as that of others has shown the high incidence of conduction disturbances following repair of ventricular defects.

Reemtsma, Copenhaver & Creech (93) have studied embryonic hearts in order to determine the site of the conduction system in individuals with membranous ventricular defects. Their studies demonstrated the bundle subendocardially along the posterior and inferior aspect of such defects, and approaching from the right. The left branch is a less discrete structure than the right and arborizes Hence, repair of a defect utilizing the left side of the apex of the septum is less likely to involve the conduction system.

Truex & Bishof (94) have also localized the conduction system in the presence of interventricular septal defect. Fifteen human hearts with a high defect were dissected. In a total of 12, the bundle was located in the posterior-inferior margin of the septal defect, i.e., between 6 and 11 o'clock as viewed from the right side and between 1 and 6 o'clock as viewed from the left side This work confirms the previous work of Kirklin and Creech.

Atrioventricular block is obviously a serious complication of intracardiac surgery. This type of derangement is often surgically created during repair of atrioventricular communis defects and high ventricular defects Direct stimulation by a myocardial electrode connected to a cardiac pacemaker will maintain individuals with an atrioventricular block until such time as a normal sinus mechanism is restored, usually within 2 to 3 weeks Such devices have been developed at the University of Minnesota (95) and the Cleveland Clinic (96).

Lillehei (97), in reviewing the contributions of open cardiotomy to the correction of congenital and acquired cardiac disease, has reported 200 cases of ventricular septal defects repaired under direct vision. The majority of his experience has been with children under 15 years of age. He stresses that the operative risk is directly proportional to the degree of pulmonary hypertension. The dividing line seems to be when the pulmonary hypertension reaches 70 per cent of the systemic tension His operative risk in those with pulmonary artery pressures below this figure has been 2 to 3 per cent. There has been a marked rise in risk when pulmonary artery pressures exceed 70 per cent of systemic pressure Heart block has been observed in 10 per cent of those having ventricular septal defects or tetralogy of Fallot corrected, and in 20 per cent of those with ostium primum lesions. A myocardial electrode is routinely used in these individuals.

Cooley, Latson & Keats (82) have reported 110 patients operated on for ventricular septal defects. Seventy-seven of these cases were reported in detail. There were 14 deaths in this initial series, an overall mortality of 18 per cent. These authors stress that operative mortality is significantly higher in those under two years of age (28 per cent), as opposed to 11 per cent mortality in those over two years This same higher mortality in the younger age group has been observed by Lam (78). Overall mortality in 58 patients operated on for IVSD was 33 per cent. However, in those three years of age or over (21 cases), the mortality has been 5 per cent.

TETRALOGY OF FALLOT

Surgery for tetralogy of Fallot is currently undergoing a significant change. Until the very recent past, shunt operations originally described by Blalock and Potts have had widespread usage. Increasing use of extracorporeal circulation and open heart technique has permitted complete correction of the existing anomalies Lillehei (97, 99), Lam (78), Cooley (98), and Kirklin (100) have all advocated open correction Operative mortality in these experienced hands now ranges from 10 to 20 per cent.

In an attempt to compare the results of open procedures with shunt procedures, the section on cardiovascular surgery of the American College of Chest Physicians (101) compiled figures from various sources. Two thousand shunt operations resulted in 18 per cent early and late deaths Two hundred thirty-eight patients who had valvotomies sustained a 19 per cent mortality. Infundibulectomy was accomplished in 67 patients with a 26 per cent mortality. As of the time of this report, 122 open procedures had been accomplished with an overall mortality of 39 per cent. This would tend to suggest that shunt procedures were still the treatment of choice; however, there has been a significantly higher improvement in the survivors of open surgery, approaching 100 per cent, which has not been observed in those having a palliative shunt procedure Further, the operative mortality in open surgery is steadily being reduced. It is of importance to note that there has been a 95 per cent operative mortality when open correction has been attempted by inexperienced personnel The favorable figures reported for shunt procedures in this report are at variance with the observations of Lillehei and Brock (102, 103) both of whom report only 40 per cent satisfactory results with these types of operations.

INTRACARDIAC TUMORS

Additional reports are now appearing of successful removal of intracardiac neoplasms Coates & Drake (104) described a myxoma of the right atrium with an intermittent shunt through a patent foramen ovale Catheterization findings resembled Ebstein's syndrome. A definitive diagnosis was made by angiocardiography, and the tumor was successfully removed, using open heart technique. Gerbode and his associates (105) have also successfully removed a myxoma from the left atrium, using extracorporeal circulation and cardiac arrest with potassium citrate. Scannel & Grillo (106)

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Lillehei (97), in reviewing the contributions of open cardiotomy to the correction of congenital and acquired cardiac disease, has reported 200 cases of ventricular septal defects repaired under direct vision. The majority of his experience has been with children under 15 years of age. He stresses that the operative risk is directly proportional to the degree of pulmonary hypertension. The dividing line seems to be when the pulmonary hypertension reaches 70 per cent of the systemic tension His operative risk in those with pulmonary artery pressures below this figure has been 2 to 3 per cent. There has been a marked rise in risk when pulmonary artery pressures exceed 70 per cent of systemic pressure. Heart block has been observed in 10 per cent of those having ventricular septal defects or tetralogy of Fallot corrected, and in 20 per cent of those with ostium primum lesions A myocardial electrode is routinely used in these individuals.

demonstrated similar flow rates 33 days later. A third group, in addition to having internal mammary artery ligation, had all branches of the subclavian vessels ligated. Flow determinations 46 days later indicated 10 cc. flow per min. The mortality in all groups, following ligation of the anterior descending coronary artery, was 78, 93 and 92 per cent, respectively. This compared with a control study with 70 per cent mortality. They have concluded that even though blood flow through the internal mammary vessels was increased in a chronic preparation with concomitant ligation of the remaining branches of the subclavian, no additional protection was offered to the animals. It is believed that little evidence exists for this procedure as mechanism of increasing myocardial blood flow.

Our experience is comprised of 34 patients, all of whom had bilateral internal mammary artery ligation performed under local anesthesia. They have been followed from 5 to 11 months after operation. Five patients have noted very slight improvement, 11 claim mild to moderate improvement, and only 1 patient is free of angina. Seven patients died of their disease 1 to 9 months following ligation. The remaining 10 are unimproved

Vineberg & MacMillan (114) have studied 7 human hearts at autopsy, 60 hr. to 18 months after an internal mammary artery implantation. In 6 of the 7 hearts, the implanted artery was patent. In the specimen obtained 18 months after operation, the implant was patent, contained little intimal proliferation, and showed evidence of branching Their overall clinical results indicate that 75 per cent of their survivors have been relieved of angina. Vineberg has again stressed that ischemia is a prerequisite for success of this type of surgery, both in the clinical and experimental efforts. Duchesne & Vineberg (115) have developed a cylinder made of an hygroscopic plastic (Ameroid). When placed about coronary vessels, these cylinders produced gradual and progressive occlusion with subsequent death of all control animals. This method was supplemented by internal mammary artery transplantation in 20 dogs Eighty-five per cent "take" occurred in this group of dogs compared with only 50 per cent "take" in a series of animals without pre-existing ischemia Other authors have reported markedly divergent results following implantation of arteries into the ventricular myocardium. Fuquay and his associates (116) implanted both internal mammary and subclavian arteries in dogs Their study suggested that protection was afforded these animals following left coronary ligation There was no marked difference in the protective quality of either of the implants. The subclavian vessels remained patent in a larger percentage of this series as a result of less intimal proliferation Survival was dependent upon the patency of the implant Patt *et al* (117) were able to maintain successful implants in 1 of 19 dogs and 1 of 25 pigs Intimal proliferation occurred in all other instances Nachlas *et al* (118) evaluated the effect of trauma on the transplanted vessel. Fourteen dogs had carotid vessels implanted in the myocardium, and 13 of these had marked decrease in patency at the end of one month, largely as a result of intimal proliferation An additional 15 dogs had the same vessel

present the third recorded instance of a successful removal of a myxoma from the left atrium. They did this under inflow occlusion, using hypothermia. A second case was also reported by Scannel of the removal of a fibrosarcoma of the right atrium. Partial atrial excision was necessary to circumvent this tumor and was accomplished without the benefit of by-pass or hypothermia.

CORONARY ARTERY DISEASE

A quarter century devoted to the study of coronary heart disease has led Dr. Claude Beck and his associates (107, 108) to certain axioms with regard to the hemodynamic principles of this disease. Some of these follow: the fate of the myocardium depends on the amount of blood available to the ischemic area; complete occlusion of one branch of the coronary artery does not necessarily result in infarction, yet infarction may occur without complete occlusion; myocardial integrity may be preserved even when the lumen has been profoundly reduced, providing there is adequate intercoronary collateral; the symptoms of coronary disease are not necessarily correlated with the total inflow. Generally, it is the uniformity of distribution rather than the total amount of inflow that determines clinical manifestations. Hence, there are three dominant causes of death in the presence of coronary heart disease: first, an unstable electrical condition associated with a lack of uniform distribution; second, a marked reduction of total coronary artery inflow; third, muscle destruction. One of the above causes is usually dominant, the other factors may contribute.

Gorlin (109) is currently perfecting a technique that will accurately measure the coronary blood flow in the intact patient. This may revolutionize our concepts of coronary artery disease, and remove from the realm of speculation the various factors which contribute to symptoms and death from coronary ischemia.

During the past 18 months, there has been considerable interest in the results of bilateral internal mammary artery ligation. This procedure was introduced in this country by Glover. He and his associates (110) have now operated on 92 patients. Fifty of these patients have been followed from 1 to 5 months Eighteen patients (36 per cent) are symptom free, and an additional 17 (32 per cent) have been benefited. Thirty-two per cent of the patients are unimproved. Improvement, as evidenced by electrocardiographic and ballistocardiographic changes, has been observed in 22 patients (42 per cent) Various groups (111, 112) have made controlled studies to see if mammary artery ligation is more effective than "sham" operations (all steps without artery ligation). The consensus is that similar improve- [illegible]

[illegible]

accomplished in the first group, and flow determined immediately. The flow was of the order of 3 cc. per min. A second group, [illegible]

GREAT VESSEL ANOMALIES

Cooley & Ochsner (125) have reviewed the various forms of total anomalous venous drainage. Most commonly all four pulmonary veins collect in one vessel situated posterior to the atria. This drains into the innominate vein through what is thought to be a persistent left superior vena cava. This, in effect, creates a total left-to-right shunt and is incompatible with life unless there is an accompanying interatrial septal defect. The authors have successfully treated such an anomaly in a six-month-old infant Correction was accomplished under hypothermia by anastomosing the common trunk posteriorly with the posterior aspect of the right and left atrium The common trunk was then divided proximal to the innominate vein, and the interatrial septum was transposed to the right of the newly created anastomosis, thus diverting the entire pulmonary venous return into the left side of the heart.

A number of similar operations have been performed and will soon find their way to publication. A recent personal experience at the Peter Bent Brigham Hospital points up the danger of pulmonary vascular disease in these patients who have reached adulthood. A perfect technical correction was incompatible with survival, as a result of old pulmonary artery thrombosis and pulmonary arteriolar sclerosis. When the pulmonary pressure and flow were restored to normal, the patient could not oxygenate his blood and succumbed. If correction is to be successful, it must antedate these changes

Creech *et al.* (126) have reported an unsuccessful attempt to correct a complete transposition of the great vessels in a nine-month infant. A kidney-shaped Ivalon prosthesis was placed in a surgically created common atrium, so that caval return was directed through the mitral valve and pulmonary venous return through the tricuspid value Cardiac by-pass with elective asystole was used. Pulmonary complications compromised a completely adequate technical procedure

Riberi & Moore (127, 128) have demonstrated that endothelial lined tubes made from free segments of pericardium were impracticable when employed experimentally to replace portions of the superior vena cava in dogs Subsequent experience with a pedicled graft constructed from the right atrial wall and appendage has been more successful This method, which permits reception of larger portions of the superior cava, has been accomplished in 24 dogs without immediate mortality.

AORTIC AND PERIPHERAL VASCULAR SURGERY

Synthetic Vascular Prostheses

Martinez, Dahl & Grindlay (129) placed Ivalon tubes in the abdominal aorta of 22 dogs These prostheses were evaluated 6 hr to 6 weeks after placement. A thrombus lines the prosthesis within 6 hr and then is thickened by superimposition of additional thrombus There is slow invasion by fibroblasts from the ends of the graft An endothelial lining covering the thrombus also proliferates from the host aorta. Dense collagenous connective tissue

implanted, but the lumen was placed into the right ventricular chamber. All of these dogs maintained patent vessels up to 10 months. Nachlas *et al.* conclude that trauma to the vessel as such is not a factor, but rather that patency is a function of continuation of flow.

Coronary artery endarterectomy as suggested by Bailey (119) is probably of very limited value, largely because of the diffuse nature of coronary atherosclerosis.

Sabiston & Fonkalsrud (120) inserted arterial homografts and nylon prostheses from the aorta to the left ventricular myocardium in 18 animals. Graft patency was observed up to 44 days, and, thereafter, thrombosis resulted. There was no evidence of arterial communication between graft and coronary arteries. Moore & Riberi (121) have reported a method of anastomosing the subclavian artery to the left circumflex coronary artery over a polyethylene stent. This technique has been accomplished in 20 dogs, with 100 per cent immediate survival.

Lord and his co-workers (122) have suggested that operations for revascularization of the myocardium be studied by measuring the the coronary blood flow, using extracorporeal circulation. The authors establish extracorporeal circulation, with total venous inflow occlusion. A Foley catheter inserted through a right ventriculotomy is advanced into the pulmonary outflow tract. The Foley catheter is equipped with drainage holes between the end of the catheter and the bag. When the bag has been inflated and the aorta cross clamped, any blood flow collected represents that coming from the coronary sinus and the Thebesian system.

Belman & Frank (123) have accomplished direct angiography of the coronary tree by injecting diatrizoate sodium (Hypaque) into a branch of the anterior descending vessel. Adequate visualization is accomplished Electrocardiographic changes coincident with the injection are manifested by T-wave depression. The same alteration is noted following saline injection and is thought to be caused by blood displacement rather than by toxicity of the contrast medium. Prolonged injection or injection into an hypoxic heart will result in ventricular fibrillation. The suggestion is made that this is an acceptable procedure when the coronary vessels are directly exposed.

Case *et al.* (124) have presented evidence to show that flow in an anomalous left coronary artery arising from the pulmonary artery is retrograde from the coronary vessel into the pulmonary artery. The source of blood is thought to be from intercoronary anastomoses arising from the normally placed right coronary artery. In view of the high mortality associated with this anomaly, operation is recommended in all patients If temporary occlusion of the left coronary vessel results in improved appearance of the myocardium and enlargement of the anomalous vessel, permanent ligation should be done. If these changes are not observed, it is suggested that creation of pulmonic stenosis may reverse the gradient. Ligation of the left coronary has been accomplished in three instances by surgeons other than the authors, with survival in one for four months.

whereas the Teflon grafts remained intact and the animals succumbed to peritonitis.

Autogenous, Homologous, and Heterologous Grafts

Jones & Dale (138) have placed 42 autogenous vein grafts in peripheral segments of the femoral arteries of dogs. Long-term patency up to two years has been observed in 60 per cent. Additional technical experience has permitted success in 80 per cent. Minor dilatation has been noted but no aneurysm formation. The veins have remained endothelialized and viable without loss of muscle, but with some decrease in elastic tissue. This technique has been employed successfully in one clinical case. Morton & Mahoney (139) were unsuccessful in accomplishing venous and arterial heterografts from pigs into the abdominal aorta of dogs Despite external support with Ivalon sponge, the venous grafts showed aneurysmal dilatation. A high failure rate was observed in both types of preparations.

Barnes *et al.* (140) have reviewed their experience with 165 aortic homografts at the Mayo Clinic. Seventeen deaths occurred, 10 of which were caused by graft failure. Nine of the graft failures were autopsied. In three, the graft had ruptured, and in six the patients had died from hemorrhage along the suture line. Factors contributing to these failures included intrinsic disease of the graft, disproportion between host aorta and graft, and poor quality of the host aorta. Technical error could not be excluded. Brown, Huggins & Koth (141) have noted that fresh autogenous grafts and freeze-dried homografts functioned equally well when used to replace segments of carotid arteries in dogs. Freeze-dried autogenous grafts were less satisfactory.

Aortic Surgery

McGoon, Edwards & Kirklin (142) report the successful excision of an aortic sinus aneurysm with an associated high interventricular septal defect, occurring in a 26-year-old female patient Direct vision, utilizing extracorporeal circulation, was used. The aneurysm was excised, and it, along with the small ventricular septal defect, was closed with a compressed Ivalon sponge The underlying pathology is believed to be a failure of the media of the aorta to join with the aortic ring A traumatic rupture of the right sinus of Valsalva into the right ventricle was repaired through a right ventriculotomy, during total cardiopulmonary by-pass with potassium arrest, by King & Shumacker (143).

Skall-Jensen (144) has reported successful closure of a congenital aorticopulmonary fistula during an open procedure in a four-month-old child. A seven-year-old male with the same defect succumbed 22 hr after operation as a result of hemorrhage A review of the world literature reveals 62 cases, only 5 of whom survived beyond the age of 15 and none beyond the age of 30. Ellis, Kirklin & Bruwer (145) have explored 20 aneurysms of the thoracic aorta Five were found to involve the proximal aorta or the arch and were not resected Of the remaining 15, 10 survived resection

surrounds the graft; however, except at the suture line, connective tissue did not invade.

Eiken, Wulff & Hallen (130) placed Ivalon, Grilon, and nylon foil prostheses in the abdominal aorta of 25 dogs. Both the Ivalon and Grilon were well tolerated. An intimalike layer developed and infiltrated the mesh to meet fibrous tissue growing from the outside. The nonpermeable nylon foil was not incorporated into the host tissues. Ivalon and Grilon were not acceptable if the segments were long, or if the diameters were less than 5 to 6 mm. Gwathmey, Pierpont & Blades (131) report satisfactory experimental and clinical results with heat sealed grafts of dacron taffeta. Five bifurcation grafts have been well tolerated in humans. The principal advantage of this material is that it can be tailored at the operating table to meet individual needs. Crawford, DeBakey & Cooley (132) have reviewed their use of synthetic material substitutes in 317 patients The functional results with nylon, dacron, Edwards-Tapp tube, nylon and dacron knit were comparable to those obtained with homografts. Orlon fabric was unacceptable because of its consistency, and Ivalon demonstrated a high incidence of thrombosis

Edwards & Lyons (133) have reviewed three years experience with peripheral arterial grafts of crimped nylon and Teflon (polytetrafluoroethylene resin). Forty-four nylon and seven Teflon grafts have been placed during this period. Acute thrombosis has occurred in seven and late occlusion in four. The limitations of nylon tubes include the necessity for heat sealing and the loss of tensile strength This latter objection can be overcome if 210 denier nylon is used, which will lose only 20 to 30 per cent of its original strength. Teflon, however, is believed to be superior because of indestructibility and chemical inertness. In addition, Teflon tubes permit development of an intimal lining within 1 to 2 months as opposed to 4 to 6 months for comparable nylon prostheses. Merendino and his associates (134) have had excellent results with seamless Teflon tubes placed in the abdominal aortas of nine human beings.

Perhaps the most critical and extensive evaluation of synthetic materials is that of Harrison (135, 136) Prostheses of nylon, dacron, orlon, Ivalon sponge, and Teflon were placed in the peripheral vessels of 133 dogs. Teflon was noted to be the most satisfactory material The advantages noted were substantially those noted by other authors, namely, chemical inertness, indestructibility, adaptability, and maintenance of tensile strength. In addition, there was an occlusive rate of only 6 3 per cent as opposed to that observed in control homografts of 10 per cent All of these prostheses were found unsuitable if the diameter of the vessel was 5 mm or less. A comparable series was carried out, replacing segments of the aorta Occlusion did not occur with any of the graft material, but again Teflon proved most desirable. Harrison has also compared the efficacy of homografts and woven Teflon tubes in replacing aortic segments when placed in infected wounds in 41 dogs (137). The complication rate in both series was of the same order (50 per cent). However, the homograft animals died of exsanguination,

the contrast medium. Huger *et al.* (151) have also evaluated the effect of 70 per cent sodium acetrizoate during aortography. One cc./kg. of the substance was injected into the aorta between balloons obstructing the aorta above and below the renal arteries. This dosage regularly caused moderate to severe nephrosis, and often paralysis. The injection of procaine (25 mg./kg.) 30 to 90 sec before injecting the test dose usually prevented significant renal injury and did, in each instance, prevent paralysis.

COARCTATION OF THE AORTA

Lemmon & Bailey (152) have suggested a new classification for coarctation:

Type I	coarctation with a ligamentum arteriosum
Type II	coarctation with shunt either proximal or distal (a patent ductus arteriosus)
Type III	coarctation with hypoplasia
Type IV	coarctation with interruption (isthmus)
Type V	coarctation, site elsewhere (specified) (*a*) ascending (*b*) arch (*c*) descending (*d*) multiple

They believe this classification is less confusing than others currently employed.

Brynolf, Crafoord, & Mannheimer (153) describe the first successful correction of an anomalous coarctation of the aorta wherein there was a persistent right aortic arch with a left descending aorta. Both carotids arose from the aorta proximal to the coarctation, and both subclavian arteries arose independently distal to the coarctation. The coarctation lay posterior to the esophagus and trachea Successful resection of the coarctation was accomplished An end-to-end anastomosis was constructed anterior to the trachea

PATENT DUCTUS ARTERIOSUS

There is agreement that, once the diagnosis of patent ductus arteriosus has been established, consideration must be given to surgical obliteration. Clatworthy & McDonald (154) have reviewed 66 patients with patent ductus proven either by catheterization, operation, or autopsy. Sixty-three of these patients have undergone surgical correction without death or postoperative complications of serious nature. Life threatening complications include heart failure, pulmonary hypertension, endarteritis, and degenerative vascular changes These changes generally do not occur prior to five years of age and have a sharp increase thereafter The authors recommend division of a ductus prior to the age of five, whether or not the child is symptomatic.

Strauss, Abrams & Robinson (155) have studied the radiologic aspects of individuals who have had surgical obliteration of a patent ductus. Seventy-one cases were analyzed both preoperatively and postoperatively The significant findings were a diminution in heart size and in pulmonary

Gerbode *et al.* (146) have presented a discussion of traumatic aneurysms of the aorta with specific reference to the fixed points in the course of this vessel. Specifically, fixation occurs at the base of the heart, at the point of origin of the head vessels, and at the esophageal foramen. A satisfactory result has been obtained in three of four cases treated by excision and homografting. Partial cardiac by-pass was utilized. Blood obtained from a left atrial catheter was passed through a roller pump and reintroduced into the femoral artery. The one unsuccessful case was caused by hemorrhage. No renal or neurological deficits were noted. Experimental work in dogs shows that flow rates of 15 cc. per kg. distal to aortic cross clamping are adequate to prevent neurologic deficits.

Experience with six cases suggests to Eiseman & Rainer (147) that the clinical management of post-traumatic rupture of the thoracic aorta should include early thoracotomy if incomplete laceration is suspected. Careful inspection and palpation of the aorta are indicated, and exploratory aortotomy may be necessary. Since an asymptomatic period of two to three weeks may elapse following injury, close observation is mandatory. There is commonly a short (1- to 36-hr.) period of lesser leak prior to exsanguinating hemorrhage. Immediate thoracotomy is indicated at this time.

Cross clamping of the thoracic aorta in the absence of a well-developed collateral will frequently cause an intolerable degree of hypertension and cardiac dilatation proximal to the site of obstruction. Experimental work by Gobbel and his colleagues (148) has shown that this cardiac dilatation and hypertension can be obviated by simultaneously cross clamping the inferior vena cava just above the diaphragm. This combination has permitted maintenance of a normotensive state in the proximal thoracic aorta.

An additional technical aid has been described by Tibbs & Leslie (149). Specially designed ring anastomosis clamps approximate the host vessel and graft over an ice cone. A water-tight seal is accomplished and maintained until suture anastomosis can be accomplished leisurely. The ice cone is rapidly dissolved, and the patency of the vessel and graft is promptly restored. The time interval between interruption and reconstitution of flow may be as short as 1 min This method has been utilized clinically, on one occasion, with bilateral anastomosis accomplished between the superficial femoral and mid-popliteal arteries. Considerable dexterity is necessary, however, a personal demonstration by the author has convinced us of the feasibility of this technique.

AORTOGRAPHY

Beall *et al.* (150) have evaluated the complications of aortography in studies on dogs and patients The contrast medium used was 70 per cent sodium acetrizoate (Urokon). Up to 30 cc. are well tolerated without evi- [illegible]

lowed one to four years without evidence of constrictive pericarditis. We agree with such initial therapy for direct cardiac trauma and resultant tamponade (162). Experience with well over 2000 heart operations leads us to conclude that the danger of constrictive pericarditis after heart surgery is neglible. It is important, however, to drain the pericardium well after any intrapericardial procedure

Bailey and his associates (163) have presented a technique for partial excision of a ventricular aneurysm. The authors recommend that symptomatic ventricular aneurysms be surgically excised.

CARDIAC TRANSPLANTATION

Blanco and his associates (164) have accomplished complete homotransplantation of canine hearts and lungs. Their technique involved cardiac arrest of the donor heart with potassium citrate, with the recipient animals maintained on extracorporeal circulation while both cavae, aorta, and trachea were anastomosed. Six of eight experiments were successful in restoring cardiac contraction with maintenance of the systemic circulation for a period of ½ to 4½ hr. (average 2½ hr). In two dogs, spontaneous respiration appeared Death in each instance followed progressive weakening of the cardiac contraction followed by ventricular fibrillation.

Webb & Howard (165) have also successfully transplanted canine heart-lung homografts in six instances Survival was observed for periods of 75 min. to 22 hr. Spontaneous respirations were never restored, suggesting that transplantation of both lungs is not feasible.

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vasculature which was observed in the majority of instances. The earliest changes occurred in the pulmonary artery and later in the overall dimensions of the heart. In the event that these changes did not occur within 6 months, a complicating lesion should be suspected.

PERIPHERAL ARTERIAL SURGERY

Gurdjian & Webster (156) have reported five patients with neurological changes proven clinically to be caused by obstruction of the carotid system at the carotid bifurcation. Endarterectomy was accomplished in all patients, with four showing improvement. Deterling (157) has observed a high order of success, using permanent by-pass grafts in the treatment of occlusive arterial disease. Thirty-one of 39 homografts inserted between the femoral and popliteal arteries remained patent. Six of seven grafts from the iliac arteries distal functioned adequately, and five of eight bifurcation grafts were successful. One long aortic coarctation was by-passed successfully. However, a by-pass from ascending to descending aorta resulted in a fatality. Synthetic woven grafts employed in 10 patients for replacement of peripheral arterial segments were only 50 per cent successful, largely because of the limitations of the underlying disease. Cannon, Barker & Kawakami (158) have reviewed the results in 59 patients who underwent femoral and popliteal endarterectomy for obliterative atherosclerosis. Satisfactory results were achieved in 66 per cent, who demonstrated patency of the arterial tree distal to the site of endarterectomy. These authors conclude that direct surgery is contraindicated unless distal patency exists.

Muller and his associates (159) have noted significantly better results with endarterectomy for obliterative arterial disease than they have with the use of grafts. Seventy per cent of 32 patients followed six months or more, who had aortic or iliac artery occlusion, and a comparable percentage of those with femoral popliteal artery occlusion had excellent results. The figures for the grafted group were 53 and 25 per cent

Jahnke (160) reports a late follow-up of 115 patients who underwent arterial repair during the Korean conflict. Arteriography demonstrated thrombosis in 33 limbs. No amputation had been necessary. Thrombosis had occurred in 18 per cent of direct anastomoses, in 44 per cent of lateral repairs, 47 per cent in which an autogenous vein graft had been inserted, and in 71 per cent in which the segment was replaced by an homologous arterial graft. Factors implicated in the poor results included tension of the suture line constriction, infection, secondary hemorrhage, or the use of a damaged vein as a graft

CARDIAC TRAUMA

Royster & Bosher (161) have reviewed 17 consecutive cases of cardiac tamponade. Thirteen patients were treated by aspiration alone, and four also underwent thoracotomy. In two instances, the bleeding point had sealed when it was visualized directly Eight of these patients have now been fol-

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NUTRITION AND NUTRITIONAL DISEASES[1,2]

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So widespread in medicine are the implications and ramifications of nutrition that it is quite impossible for any review to include all the significant advances made in the past year. To make arbitrary selection of broad categories provides one solution to the dilemma facing the reviewer, and while this choice is calculated to provide a general perspective of recent events, it is inevitable that certain obvious omissions will occur.

An appropriate note on which to begin is the occasion of the fiftieth anniversary of the American Institute of Nutrition, an event commemorated by a series of special articles [Federation Proceedings (1958)], in which past accomplishments are reviewed and directions for future progress appraised. In accordance with the perspective set forth there, let it be agreed that classical nutritional syndromes such as beriberi, rickets, pellagra, and scurvy are now only rarely encountered even in poverty-stricken areas of the world. Their absence from the present-day American scene is a testimony to medical progress and, while they rightly deserve a place in the textbook as historic landmarks, they have ceased to exist as major problems because of fortunate circumstances such as a high national economy, skilled food technology, ready accessibility to a wide variety of foods, and because of measures such as the fortification or enrichment of foods (especially grain products) and the common use of vitamin supplements

The rareness with which the classic nutritional deficiency syndromes are now encountered can lead to a false assumption that any danger of nutritional deficiency is remote. In actuality, normal nutritional function permeates all fields of modern medicine, and an awareness of its continuing and pervasive importance is fundamental to medical practice A brief review of the cellular functions of the vitamins suffices to establish the indispensability of these nutrients—thiamine is essential for the metabolism of pyruvate; riboflavin and niacin are involved in hydrogen transport; pyridoxine plays an important role in many aspects of amino acid metabolism, including transamination and decarboxylation, folic acid and cyanocobalamin (B_{12}) enter into nucleoprotein metabolism; the integrity of connective tissue depends in part upon ascorbic acid, synthesis of prothrombin requires vitamin K; calcium and phosphorus utilization are regulated by vitamin D; and vitamin A is involved in the regeneration of rhodopsin, the visual

[1] The survey of literature pertaining to this review was completed in August, 1958.

[2] The following abbreviations will be used: BAL (2,3-dimercaptopropanol); EDTA (ethylenediamine tetraacetic acid); Na_2EDTA (disodium ethylenediamine tetraacetic acid).

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achylia, reduction in absorbing surface, biliary disease; (*d*) impaired metabolic utilization—liver disease, hypothyroidism, diabetes mellitus, malignancy; (*e*) increased loss—polyuria, hemorrhage, negative nitrogen balance, decubitus.

From a report on nutritional status in the Near and Far East [Berry & Schaefer (17)] it appears that caloric, protein, thiamine, ascorbic acid, and vitamin A deficiency symptoms may still occur in this twentieth century whenever the food available is limited in quantity, variety, or biologic value, and when national customs or habits make change difficult to accomplish. For such surveys of populations, proven methods for nutritional appraisal (dietary, biochemical, and clinical) have been developed and are described in a recent manual (18). The section on clinical appraisal is quite adaptable to clinic or private practice, however, and it utilizable as a practical measure in the ordinary physical examination [originally adapted from Jolliffe (19)].

The converse.—Within the past few years it has been realized that nutritional excesses as well as deficiencies call for recognition and prevention.

TABLE 1

OUTLINE OF MAJOR NUTRITIONAL DEFICIENCY SIGNS*

Nutrient	Abnormal Clinical Sign
Calories	Obesity — Skin Thickness
	Scapulae: over 30 mm.
	Lower axillae: over 25 mm.
	Height-Weight Tables over 10 per cent
	Leanness—Skin Thickness
	Scapulae. under 8 mm.
	Lower axillae: under 8 mm.
	Height-Weight Tables: under 10 per cent
Protein	Dependent edema
Vitamin A	*Follicular keratosis of arms*
Thiamine	Absent Achilles tendon reflexes
Niacin	Tongue lesion more advanced than hypertrophy of papillae at tip
	Reddened tongue
	Pellagrous dermatitis
Riboflavin	Angular stomatitis
	Conjunctival hyperemia
	(Circumcorneal injection)
	Magenta tongue
Ascorbic Acid	Red *hyperemic gums*
	Perifolliculosis

* Adapted, with permission, from "Manual for Nutrition Surveys," Interdepartmental Committee on Nutrition for National Defense, 1957, Supt of Documents, Wash. D.C.

pigment of the rod cells of the retina. Several of the foregoing functions are examples of the coenzyme roles played by many of the vitamins.

Broad Nutritional Problems

The consequences of limiting or interfering with these normal cellular processes can still be observed at the clinical level, but in guises quite different from the classic deficiency states. While the basic cause remains the same—an inadequate supply of nutrients—the circumstances have changed. For example, a certain "side-effect" of a drug may be in reality a nutritional deficiency symptom arising secondarily to the antimetabolite or antibacterial property of the drug. One example is the peripheral neuropathy or epileptiform seizures that may be encountered during isoniazid therapy (1 to 6). These have been shown to reflect a pyridoxine deficiency state caused by the inactivation of this vitamin by the hydrazide group of compounds (semicarbazide, thiosemicarbazide, and isonicotinylhydrazide). Another example is seen in the mucous membrane lesions encountered during protracted sulfonamide or antibiotic therapy, a consequence of the suppression of the normal bacterial flora of the mouth and large intestine, resulting in B complex deficiency (7, 8, 9). Prolonged high doses of salicylates can lead to hypoprothrombinemia by a similar mechanism. Employment of chelation therapy (EDTA) has been reported to result in pyridoxine-deficiencylike lesions (10). Other drug-induced deficiency states can be cited However, there are more common conditions in which the physician encounters modern problems of nutrition The alcoholic and the drug addict by persistent omission of protective foods from the diet, often exhibit a mixture of nutritional deficiency signs and symptoms The food faddist and the chronic weight reducer may find himself in a borderline nutritional state The pace and social custom of city life harbor dietary imbalance. Poverty, apathy, and adentia contribute to the nutritional problems of the aged.

It is apparent that the possibility of subclinical nutritional deficiency still requires recognition and prevention Adequate protein of high biologic value must be assured for maintenance and repair of tissue. Supplementary vitamins provide a desirable safeguard [Jolliffe (11), Goodhart (12)] but there are certain rational indications for their use [Darby (13), AMA Council on Foods and Nutrition (14)]. Maintenance formulas of vitamins should approximate, but not greatly exceed, the amounts described in the 1958 Recommended Dietary Allowances for vitamins [National Research Council (15)]. A suitable therapeutic vitamin formula is provided by three to five-fold the quantities for maintenance Such a formulation has been described in detail [National Research Council (16)] and is justified in the following conditions. (*a*) diminished intake—anorexia, adentia, certain therapeutic diets, certain gastrointestinal disorders, and pre- and postoperative interdiction of food by mouth; (*b*) increased requirements for nutrients—growth, physical exertion, pregnancy, lactation, fever, hyperthyroidism; (*c*) impaired absorption—hypermotility of gastrointestinal tract, achlorhydria or

higher in myocardial infarction patients (as a group) than in the corresponding average for similar aged groups in each sex who do not have overt manifestations of atherosclerosis; (*c*) individual differences are so great that neither the cholesterol nor lipoprotein level in any individual case can be viewed with certainty as a premonitory sign of present or future coronary disease.

Dietary fat has, in turn, been scrutinized in terms of saturated versus unsaturated fatty acid content. It was demonstrated that the intake of saturated fatty acids can have a definite effect upon blood cholesterol levels (32 to 35). It appears that the unsaturated type of fatty acid (specifically linoleic and probably arachidonic) can produce a fall in blood cholesterol in the presence of (*a*) lowered total fat intake and (*b*) lowered proportion of saturated fatty acids. Less definite have been the results obtained when unsaturated fats are merely added to the normal diet without concurrent reduction in both the total fat content and the proportion of saturated fatty acids (36, 37). This is possibly the result of the cholesterol-raising effect of a positive caloric balance (38) Other questions have arisen incidentally, such as that pertaining to the slight superiority for lowering cholesterol levels exhibited by corn oil over other vegetable oils which have a higher content of unsaturated fatty acids (39).

Controversy over the ability of unsaturated fatty acids to lower hypercholesterolemic blood levels has been resolved by the appearance of several papers demonstrating the circumstances where these are effective. These circumstances are essentially those of careful dietary control and feature: (*a*) decrease in the intake of animal (saturated) fat; (*b*) increase in the intake of certain vegetable (unsaturated) fats; (*c*) avoidance of weight gain. It now seems well established that when saturated and unsaturated fats are consumed together in special formula diets, the hypercholesterolemic tendency of each gram of saturated fat can be offset by approximately 3 gm. of unsaturated fat [Bronte-Stewart *et al* (40), Beveridge *et al* (41), Ahrens *et al* (42)]. Recent studies show lowered blood cholesterol levels can also be attained on an outpatient basis (i.e , without use of formula diets) by either of two measures· (*a*) low-fat diet, (*b*) vegetable oil, plus low saturated (animal) fat. The results to be expected from these two approaches have recently been described, as well as the further effect obtained when a quantity of unsaturated fatty acids is added to the low-fat regimen (2000 total calories in the diet). By such a second step, a further lowering of blood cholesterol, beyond that attained by low-fat diet alone, may be possible [Brown (43)]. Similar conclusions have been reported in a group of patients who continued to show hypercholesterolemia following myocardial infarction despite dietary measures alone The conclusions reached in this study were that a fortified unsaturated fatty acid formula produced approximately 30 per cent lowering in the persistently elevated blood cholesterol levels, and that the amount of decrease was influenced by the type of diet (low, moderate or high fat) and concurrent gain in weight [Meltzer *et al.* (44)]. Similar results have been

Vitamins are drugs despite their natural occurrence in foods and despite an extremely low general toxicity. When employed in their crystalline or synthetic form as supplements to the diet, they require medical supervision as with any other prophylactic or therapeutic agent. Recent attention has been drawn to the dangers of excessive quantities of the fat-soluble vitamins A and D. Hypervitaminoses A and D can occur from overenthusiastic administration of pediatric vitamin formulas to infants or from routine employment of therapeutic formulas in older children and adults. Thirty-six cases of hypervitaminosis A, mostly in infants and young children (but including six adults) have been reported in one series [Oliver (20)]. Symptoms in children include anorexia, dry itchy skin, alopecia and sparse coarse hair, angular fissures or cracking of the lips, and palpable hepatomegaly. Later symptoms include painful swellings over tibia, fibula, clavicles, ulna, and metacarpals. In adults the symptoms are a more severe alopecia, skin involvement, and nail changes; exophthalmos, menstrual disturbances, and skin pigmentation are rarer symptoms. Both acute (Marie-See syndrome) and chronic symptom-complexes have been described [Jeghers & Marraro (21)].

Hypervitaminosis D can arise from the cumulative direct and indirect sources of this vitamin, including sunshine, mercury vapor lamps, vitamin D-fortified milk, and excessive use of vitamin supplements. Idiopathic hypercalcemia of infancy is one of the syndromes contributed to, or perhaps caused by, toxic quantities of vitamin D [Lowe (22)]. Other syndromes, including metastatic calcification, have also been reported [Bauer & Freyberg (23)].

Toxicity due to excesses of another of the fat-soluble vitamins, vitamin K, has been reported in the form of kernicterus resulting from high doses administered to premature infants A safe single dose, adequate to prevent hemorrhagic disease in the newborn, is approximately 1 mg. of synthetic vitamin K (menadione) (equivalent to a dose of 3 mg. menadiol sodium diphosphate) [AMA Council on Drugs (24)].

Specific Nutritional Problems

Fat and unsaturated fatty acids.—The possibility of an interrelationship between (*a*) the quantity and type of dietary fat; (*b*) blood cholesterol; and (*c*) coronary atherosclerosis has continued to command attention It will be recalled that the original impetus of this theory emerged from epidemiologic surveys on populations, civilizations, or social strata where the available statistics seemed to indicate that a relationship did exist between the incidence of coronary disease and the level of dietary fat (25, 26, 27). While this theory has been questioned by some (28), it has appeared sufficiently promising to motivate several studies of cholesterol (and lipoprotein) levels in patients with histories of myocardial infarction or angina pectoris, compared to normal individuals of similar age in each sex (29, 30, 31). The general indications which have emerged from such studies are· (*a*) serum cholesterol levels provide as dependable an index of disturbed lipide metabolism as do lipoproteins; (*b*) average cholesterol and lipoprotein levels are

ubiquity of a high-fat intake wherever there is a high rate of degenerative or occlusive vascular disease. This relationship has undergone careful scrutiny in a recent review, both in relation to the experimental approach in animals (57), and from epidemiologic standpoints (58). While it seems true that several factors may be involved in the long chain of events culminating in coronary occlusion, there is considerable support for the concept that high-fat intake (either per se, or by conversion from carbohydrate), is the basic nutritional factor leading to atherosclerosis. Whether or not this factor also favors increased blood coagulability requires further study.

Calories and obesity.—The problem of obesity is intrinsically important because of its apparent relationship to an increased death rate from any of several causes, prominent among which have been listed diabetes mellitus and cardiovascular diseases; recently, the thesis that a direct relationship exists between obesity and the development of cardiovascular disease has been challenged (59, 60, 61). In turn, a rebuttal to this challenge has been presented in an exhaustive resurvey of insurance company statistics [Gubner (54)], whence it is again asserted that a threefold increase in cardiovascular disease mortality occurs in those 30 to 39 per cent overweight, compared to those 10 to 29 per cent underweight Pathologic as well as actuarial data are cited to show that cardiovascular involvement is frequent (in both sexes) in the presence of obesity. Further, reference is made to a recent study of the rate of development of "new" coronary disease among males age 45 to 62, and among civil service employees aged 39 to 55, in which a direct relationship appeared to exist with excess weight (62) From such studies as these, the conclusion has been drawn that the individual's chance of developing coronary heart disease is considerably greater if he shows any two of the following three conditions obesity, hypercholesterolemia, hypertension It is also interesting to note that the obese individual may show an augmented and protracted postprandial rise in blood lipides, similar to that observed in diabetes (63, 64), and also reported to occur in coronary disease (65).

Although the likely relationship between obesity and cardiovascular disease has far-reaching medical implications, fatness has aroused greatest concern among the laity for reasons cosmetic rather than those pertaining to health and longevity. Innumerable "reducing plans" have been spawned as opportunistic devices which have appeal to a gullible public This has resulted in a special report on the subject of fad diets and allied evils (66). There is little to gainsay the well-established principle that the best reducing regimen is one based on long-term revision of food habits by employing a nutritionally sound diet deficient only in calories—the "Basic Diet" (67). The numerous factors involved in middle-aged obesity have been reviewed, with emphasis on the dual factors of social custom and "spectatorship" which are compounded with decreased energy output (basal metabolism declines with increasing age, as do normal exercise habits) (67). In most reducing programs, attention is usually centered on caloric input, with the outgo expenditure of energy relegated to a secondary position, caused mostly

obtained in other studies, some of which have demonstrated that the drop in cholesterol (accomplished by the addition of unsaturated fat to a low-fat diet) was accompanied by a drop also in S_f 12–400 class of lipoproteins (45). Provocative articles have appeared demonstrating a temporary drop in blood cholesterol following infusion of intravenous fat (cottonseed oil) (46), and also under other circumstances where it was possible to decrease or increase the level of cholic acid in the bile following administration of saturated versus unsaturated fatty acids, respectively [Lewis (47)]. The latter finding implies that one effect of unsaturated fatty acids is to increase the amount of cholesterol or cholesterol derivatives excreted in the bile, thereby effecting a lower level in the blood. There is, of course, the matter of reabsorption to be reckoned with, and this recalls the earlier approach of preventing absorption of both endogenous and exogenous cholesterol from the intestinal tract by employing plant sterols (sitosterol) The prevailing opinion on the effectiveness of this measure alone appears to be that it is effective for producing a modest reduction in serum cholesterol (5 to 25 per cent), provided relatively large amounts of the sitosterol are taken with each meal [*Nutrition Reviews* (48)]. The combination of vegetable oils plus sitosterol would seem to be still more effective than either alone [Farquhar & Sokolow (49)].

Evidence has appeared also to confirm the previously reported effectiveness of (*a*) large doses of nicotinic acid for lowering elevated blood cholesterol [Achor (50)], and (*b*) hydralazine or ganglionic blocking agents [Deming *et al.* (51)].

While there appears to be justification for employing any reasonable means of lowering elevated cholesterol levels in those individuals who have evidence of coronary artery disease, or diabetes, or xanthomatous conditions, the problem of arteriosclerotic vascular disease involves so many possible factors that changes in the national diet are still viewed with circumspection (52). The respective roles played by other factors such as heredity, hormones, stress, exercise, smoking, carbohydrate excess, protein deficiency, disorders of clotting, etc., yet require elucidation [Goldsmith (53)] Prevailing opinion appears to favor the view that the actual coronary occlusion may involve at least two basic processes. (*a*) atherosclerosis, and (*b*) thrombogenesis or fibrinolysis or both. The former appears to begin in the aorta and other large vessels as early as adolescence and may reflect the biologic phenomenon of "aging," perhaps being unrelated to fatness and coronary artery disease. The coronary episode, while often superimposed on the atherosclerotic process, may be caused more directly by *ad hoc* conditions such as thrombogenesis, fibrinolysis [Gubner (54)], and perhaps "sludging of blood cells" [Knisely and co-workers (55)] Engelberg (56) considers that a deficiency of circulating heparin may exist in coronary-prone individuals, and it is interesting to recall that the rate of clearance of fat from the blood, slower than normal in coronary-prone individuals, can be influenced by heparin

Despite the uncertainties which exist about these and other factors that may be involved in coronary artery disease, it is difficult to ignore the

the tissue gained during the first week of supplementation was 3.4 cal /gm., but that of the seventh week was 6.9 cal./gm. Wide differences were noted among the 12 male college student subjects in their inclination to make compensatory changes in food habits during their regular meals, some of whom demonstrated "obesity-resistance"—others "obesity-proneness." Observations of blood sugar levels and rates of gastric emptying revealed that the "decreased intake of food at mealtime was not readily attributable to a glucostatic mechanism of appetite control or to a mechanism dependent upon the mechanical effects of nutrients in the gastro-intestinal tract" [Fryer (76)]. This finding offers additional evidence to that previously reported on the lack of relationship between blood glucose levels and control of appetite [Freyer (77); Bernstein & Grossman (78)].

An interesting question has been raised concerning the mechanism responsible for the lowering of hypertension commonly obtained following reduction in weight It is now pointed out that the drop in blood pressure obtained by weight reduction in eight hypertensive patients was closely correlated with the "incidental" decrease in salt intake inherent in the reduction in calories. The suggestion is therefore made that it is the decreased intake of sodium ion which is the most important factor in weight reduction regimens designed to lower blood pressure [Dahl and co-workers (70)]

Some Medical Problems Involving Nutritional Substances

Intravenous fat —Within the past year a safe and clinically useful means of providing fat intravenously has approached realization. There has been need for a concentrated source of calories to prevent the negative nitrogen and caloric balance which is incidental to the triad of increased tissue breakdown and repair in the presence of limited caloric intake. These conditions are encountered in burns, trauma, decubitus, long convalescence, and wasting disease with cachexia.

It is unlikely, of course, that any change will be effected in the obligatory catabolic phase that accompanies the immediate postsurgical or posttraumatic period, for the same reason that intravenous protein hydrolysates have only limited use during that period. However, once the anabolic phase of the recovery period begins, a means of sparing nitrogen via increased caloric intake should find a measure of clinical usefulness Furthermore, in cases of emaciation or subnutrition, both pre- and postoperatively, a concentrated source of calories would be useful Also, when intake of food by normal routes is interdicted or prevented, intravenous fat preparations would be of value. Previous efforts to fill these needs by intravenous glucose, fructose, or alcohol have all met with only partial success because of the volume of fluid involved, the phlebitis incidental to the administration of concentrated solutions, the discomfort to the patient, and the demands upon the professional staff (79).

A special symposium (80) on this subject has appeared in connection with a new fat emulsion consisting of 15 per cent cottonseed oil stabilized in

by the relatively insignificant caloric cost of exercise plus its stimulating effect upon appetite. Nevertheless, attention is periodically called to the fact that as small an expenditure as 200 calories daily for exercise would suffice over the course of a year to prevent the development of obesity in many, and would result in appreciable weight reduction in others (68). A recent study again emphasizes that as mild an exercise as walking has definite effects upon caloric balance, promotes the individual's adherence to the reducing regimen, and aids in developing general health and fitness. When seven obese adults (238 to 261 pounds) were hospitalized and placed on a 400-calorie diet, and required to walk out of doors 3 to 4 hours daily (caloric expenditure 2850 to 3590), the weekly weight loss was from 4 7 to 6.0 pounds and there were very few complaints of hunger. This last observation led to the speculation that the sensation of hunger "fades when negative caloric balance is high and the subject approaches a fasting condition." It was also reported that 90 per cent of the energy expended was derived from combustion of body fat, judging from respiratory quotients usually below 0.76. A mild ketosis implied that these patients were able to metabolize body fat more efficiently than normal individuals [Strong and coworkers (69)]. This observation can perhaps be related to a recent finding that a fat-mobilizing substance is present in the urine during fasting (*vide infra*).

While caloric input versus output is the approximate physiological equation determining gain in weight, there are nevertheless certain questions which can be raised concerning the possibility of a changed metabolic state in the obese state. First, there is an increased appetite for fat, judging from a recent survey of food habits. Also, it has been reported that obese children are less active than their lean or normal counterparts (71). Further, there is a lessened utilization of fat stores as a consequence of physical inactivity (54).

This latter problem, i e., utilization of fat stores—has been the subject of a series of studies directed at the identification of a mechanism which controls mobilization of body fat [Kekwick & Pawan (72, 73, 74)]. A recent study by this same group of investigators has demonstrated that the urine of the fasting human contains a fat-mobilizing activity (for mice) which is absent from the same individual's urine when he is not in the fasting state. This substance, upon injection into mice, resulted in a mobilization of fat from fat depots, an increase of the total metabolic turnover of fat and the total amount of fat in the liver, and caused weight loss without depressing the appetite when given over a period of time, the loss being in the form of body fat and water (75).

The implication of such studies is that there exists an endocrine or other internal mechanism which governs both deposition and mobilization of fat stores in the body. The concept that susceptibility or resistance to the development of obesity is influenced by factors other than will power alone is supported by results of a study on the effects upon body weight of a late night 1000-calorie supplement It was computed that the caloric value of

Other investigators were not impressed by the results from arginine. Doses of 25 to 37 gm. of arginine were given to 10 patients with hepatic encephalopathies; only three of the patients showed temporary improvement during infusion, although five eventually recovered in 5 to 14 days following discontinuance of therapy [Fazekas *et al.* (90)].

Fahey, Nathans & Rairigh (91) studied the effects of arginine on elevated blood levels of ammonia. L-Arginine hydrochloride was infused in doses of 30 to 39 gm. This had no consistent effect on the blood ammonia of eight patients with hepatic encephalopathy, or in six subjects with normal liver function who received infusions of ammonium chloride. Nevertheless, arginine markedly decreased the rise in blood ammonia produced by infusing glycine or an arginine-deficient mixture of amino acids.

Highly favorable results from the use of arginine were obtained in another series [Manning & Delp (92)]. Of 24 patients with ammonia intoxication treated with arginine, 11 survived Equally favorable results have been reported in a series of 50 patients [Najarian & Harper (93)]. General measures consisted of limitation of protein intake, control of gastrointestinal bleeding, prompt removal of blood from within the gastrointestinal tract and oral administration of antibiotics. In addition, arginine chloride was administered intravenously—500 cc. of a 5 per cent solution being infused over a period of 2 hr., and repeated at 8 to 12-hr. intervals as required. All except 2 of the 50 patients showed improvement.

Thus, advances appear to have been made in the *pro tem.* treatment of liver coma and associated encephalopathies While this is gratifying, it will be recalled that this emergency therapy does not affect the basic liver disease. However, recovery from the acute ammonia intoxication does permit the eventual institution of long-term measures aimed at improvement in hepatic function, together with avoidance of excessive amounts of ammonia from dietary protein, hemorrhage, etc A supportive regimen recommended by Sherlock (94) for treatment of hepatic coma is as follows. (*a*) omission of all dietary protein, (*b*) at least 1600 calories as glucose drinks or as 20 per cent glucose by the intravenous route, (*c*) during recovery, protein is added as 20 gm. increments on alternate days, this amount divided into 44 meals, (*d*) gradual attainment of normal protein commensurate with the speed of recovery; with (*e*) reduction of protein in the chronic phase, the actual amount being determined by the limits of tolerance, usually 40 to 50 gm daily; (*f*) supplements of vitamins K and B complex.

Folic acid.—The function of folic acid is often separated from that of cyanocobalamin (B_{12}) by the inability of the former to prevent the spinal cord degeneration encountered in pernicious anemia, making B_{12} the only definitive therapy for that disease. Equally puzzling, or perhaps equally indicative of the specificity of the vitamins, is the effectiveness of folic acid in the malabsorption syndrome known as tropical sprue—a disease seldom encountered in the temperate zone, and characterized by diarrhea and secondary nutritional deficiencies manifested by glossitis and macrocytic anemia Gardner (95) has presented a masterful summary of this unique

the homogenized form, lecithin (highly purified, derived from soya), and a nonionic agent acting as emulsifiers. It appears that there is agreement among a number of clinics employing this new emulsion that the caloric availability is similar to that from oral fat. However, a certain incidence of side effects has been reported from many of the clinical studies. Although chills, drop in blood pressure, back and bone pain, nausea and vomiting which had been encountered with early supplies did tend to improve with later lots, fever has remained a problem, occurring approximately as frequently as it had previously (15 per cent) (81). There is an interesting possibility that the rate of lipemia clearance is related to these thermogenic side effects (82). Reference was also made in one of the reports of this series to changes in liver function observed in burn patients who received the emulsion over a prolonged period of time. Similarly, patients with portal cirrhosis also showed increasingly abnormal liver function tests Other possible side effects apparently include widespread systemic effects incidental to hemolytic anemia and bleeding tendencies (81).

Despite these adverse findings, the general impression is obtained that this latest preparation represents a definite advance towards solving the problem of adequate intravenous caloric alimentation, and that it is relatively safe for short-term use. Ultimately, it may be possible to supply a nutritionally complete mixture of the three major classes of food, together with the requisite vitamins required for normal metabolic function. This concept is described in one of the articles of this series (82).

Intravenous amino acids (liver coma).—The relationship between blood ammonia accumulation and the encephalopathy of severe liver disease has been a controversial subject. Inconsistent results were encountered with the use of sodium glutamate alone (83 to 87) More favorable reports have appeared in connection with the employment of intravenous arginine and, most recently, arginine glutamate. The rationale for the latter combination lies in (*a*) avoidance of the sodium ion which may precipitate alkalosis, and (*b*) employment of two routes for removal of the ammonia· (i) conversion to urea via the Krebs-Henseleit cycle, and (ii) conversion to glutamine by combination with the glutamate.

Clinical studies involving the use of arginine in the treatment of hepatic encephalopathies were first published in 1956 [Najarian & Harper (88)] Doses of 25 gm. of arginine hydrochloride, infused over a period of 1 to 2 hr., reduced elevated blood levels of ammonia in 15 cases, and was followed by striking improvement in most instances.

The effects of arginine hydrochloride and sodium glutamate on toxic symptoms produced by intravenous ammonium chloride have been compared [Bessman *et al.* (89)]. Four patients (2 cirrhotic) were given infusions of ammonium chloride; during the last half of the infusion, the patients with cirrhosis showed mild toxic symptoms However, a combination of ammonium chloride with arginine hydrochloride produced milder symptoms in one cirrhotic patient, and no symptoms in the other. None of the infusions caused any toxic symptoms in either of the noncirrhotic patients

sis, copper in Wilson's hepato-lenticular disease, and zinc in porphyria. While increased urinary excretion of each of these metals can be accomplished by employment of an appropriate chelating agent, unfortunately their removal does not appear to effect a cure of the basic disease. Hemochromatosis is still treated most effectively by phlebotomy. In Wilson's disease, while enhanced excretion of copper is obtained following administration of calcium Na_2EDTA, BAL, or penicillamine, improvement in clinical status is sometimes encouraging but often it is variable. In porphyria, improvement in clinical symptoms has recently been reported following enhanced urinary excretion of zinc produced by administration of a chelator such as disodium EDTA or BAL. (99).

The ubiquity of calcium in the body, its key role in normal physiologic processes, and its predilection to deposit in aging or chronically diseased tissues, have led to a number of investigations in which EDTA has been employed for removal of this cation. Following an initial report of the successful control of blood calcium levels in animals, (100) subsequent attempts to employ EDTA in human hypercalcemia (101, 102) were unsuccessful. Nevertheless, it is quite possible to obtain anticoagulant effects from EDTA because of its calcium-chelating properties (103, 104), and when isolation of platelets is the objective, this agent appears to be superior (105). By this same mechanism of calcium chelation, EDTA can be successfully employed as an eye-drop preparation to dissolve corneal calcifications (106), and there are recent reports of correction of digitalis-induced cardiac arrythmias through the action of EDTA on ionized serum calcium which, in turn, affects the permeability of the cell to potassium (107).

Since kidney stones contain calcium, it would seem that they should be dissolved by chelating agents. Clinically, however, results have not been completely successful, mainly because of chemical irritation which arises when sodium EDTA is perfused through the ureter (108)

Conditions where specific cations are suspected —Studies have been carried out in other conditions where calcium deposition is suspected to play an indirect role in the development of clinical disease. Successful employment of EDTA in a variety of conditions associated with calcinosis led to the speculation that removal of calcium from the cardiovascular system might provide a means of treating atherosclerosis (109) A subsequent clinical report (110) described definite improvement in exercise and work performance in twenty patients with disabling angina pectoris. This improvement was accompanied in some cases by a demonstrable improvement in EKG pattern.[3] It is possible that a drop in blood cholesterol may also have oc-

[3] EKG changes in normal individuals have been reported during temporary hypocalcemia induced by Na_2EDTA (120) With an average drop in serum calcium of 1 0 to 1.7 m eq /L (=31 4 per cent), there was a shortening of the R-R interval, and a prolongation of QT However, neither T-wave flattening or inversion, nor elevation or depression of the RS-T segment was noted in that series.

condition for which several etiologic causes must be considered: (*a*) nutritional deficiency—based on the specific response obtained to folic acid during stages I and II; (*b*) infection—based on the palliative but not curative effects obtained from sulfonamide therapy (and antibiotics); (*c*) abnormal metabolism—based upon the observation that vegetable fats are employed widely in those areas where sprue exists. (It should be noted that sensitivity to wheat gluten is not a factor in tropical sprue as it is in the nontropical type. *Nor is there impaired calcium absorption, also encountered* in the nontropical variety.) Stages of the disease are well-outlined as early (fatigue, asthenia, steatorrhea), deficiency (weight loss, mucous membrane lesions reflecting B complex deficiency) and, lastly, the macrocytic anemia stage.

Minerals in Disease

While the functions of the major minerals are apparently well-delineated, little is known about the normal and abnormal functions of those which are *required in trace amounts. It is, of course, true that the functions of* Na and K in acid-base balance, and iodine and copper in relation to the thyroid hormone and hemopoiesis, respectively, have been well characterized. However, the area of nutrition involving trace metals abounds in unknown potentialities, for these substances are involved in numerous metabolic activities at the level of the cell, either as components of metallo-enzymes, or as catalysts for enzymic activity Numerous examples can be cited. Zinc is found in carbonic anhydrase, uricase, catalase, peroxidase, carbodypeptidase, lactic dehydrogenase, and alcohol dehydrogenase (96, 97). In a paper dealing with the clinical entity of porphyria (98), reference is made to the possible effects of an excess of zinc upon certain enzymatic and endocrine functions which could be ultimately involved in the basic pathology of that disease. Copper is found in uricase, tyrosinase, ascorbic acid oxidase, and laccase; its presence in the cobalamins (vitamin B_{12} series) is very well known. Molybdenum is found in nitrate reductase, xanthine oxidase, and aldehyde oxidase. Iron is involved in the structure of cytochrome, peroxidase, catalase, and hydrogenase It is apparent that the integrity of all these cellular enzymes is important for normal cellular physiology.

Trace metals act as catalysts to numerous enzymes involved in the intermediary metabolism of foodstuffs. Examples include magnesium in the process of phosphorylation, potassium in phosphotransacetylation, manganese, aluminum, cobalt, and zinc in various stages of the tricarboxylic cycle (Krebs). Metals also serve as activators of the arginase, lecithinase, deoxyribonuclease, and (histidine) deaminase systems. The importance of [illegible] systems is also self apparent.

[illegible] ditions which are characterized by accu[illegible] s) of metals which are derived endogenously. The metals do not accumulate as a result of environmental exposure but rather as a consequence of disease. Examples include the excessive deposits of iron encountered in hemochromatosis and hemosidero-

disease by employing chemical microdissection, but also by emulating certain *physiological processes which occur as part of the normal function of the* cell (121).

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curred in those treated, judging from a separate report (111) of hypocholesterolemic effects following administration of EDTA. It may be pertinent to observe that prolonged prothrombin time following the administration of EDTA has been reported by two groups (112, 113).

It is also of interest to contemplate a report in the Polish literature (114) describing results following subcutaneous administration of the disodium calcium salt of versenic acid which "lowers the level of cholesterol and fatty acids, diminishes the number of sclerotic nodules in the arterial vessels, and decreases the quantity of crystals of cholesterol digitonide and the thickness of lipid infiltrates in the arteries" of pigeons in which atherosclerosis had been previously provoked by a diet rich in cholesterol and lipides.

A provocative survey of hypothetical mechanisms which might be involved in atherosclerosis and collagen disease appears in a recent publication (115) in which an attempt is made to integrate both the basic and applied aspects of treatment with chelating agents. It was found that disodium EDTA prevented deposition of cholesterol in the liver of animals receiving a high cholesterol diet, although blood cholesterol was itself elevated. It was also reported that under similar circumstances Mg EDTA prevented both a rise of blood cholesterol and aortic plaque formation, in contrast to the results found in cholesterol-fed controls receiving no Mg EDTA. A hypothesis was developed to explain why both calcium and magnesium might be involved in the deposition of atherosclerotic plaques, and how chelating agents, by effecting subclinical hypocalcemia, could cause a removal of those cations from the plaques, and consequent dissolution of the lesions. In such a scheme, the parathyroid glands would be involved in the interchanges of calcium, and attention was drawn to the influence potentially exerted by parathormone in governing the rate of turnover of calcium and other metals that are indirectly governed by calcium.

Coincidentally, it has been suggested that both calcium and magnesium may be implicated as key substances in scleroderma. The first report drawing attention to benefits from chelation therapy in scleroderma described improvement in the skin and joints of one patient suffering from scleroderma, sclerodactylia, and calcinosis (116). Subsequently, another report (117) stated that in two scleroderma cases treated by EDTA, improved pliability of the skin occurred in one patient (with both scleroderma and dermatomyositis), but that in neither case was there discernible change in visible (x-ray) calcinosis. *Most recently, a lessening of the induration and sclerotic* appearance of the skin has been reported in three additional cases of noncalcific scleroderma (acrosclerosis) (118). Increased pliability was observed in the skin of the face, neck, and upper arms, and also an increased mobility of the larger joints. Benefit was also reported in the ulcerations of the hands and feet characteristically found in acrosclerosis.

In a recent article concerning their effectiveness as antirheumatic compounds, salicylatelike or salicylate-derived compounds are shown also to have the capacity to perform as chelators (119).

Thus, the principle of chelation may offer not only a means of studying

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ENDOCRINOLOGY (DIABETES)[1,2]

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CARBOHYDRATE AND FAT METABOLISM

Fructose.—The revival of interest in fructose metabolism in recent years stems from the fact that this sugar does not require insulin for entry into the glycolytic cycle and hence should be more readily metabolized by the diabetic organism than glucose Miller *et al* (1), among others, have reported that when given intravenously to diabetic patients fructose produces greater carbohydrate retention than glucose, and, in conjunction with insulin, is somewhat superior in raising serum CO_2 and reducing plasma acetone levels in acidosis. Similar but less striking results have been obtained by Moorhouse & Kark (2) without insulin, using the intragastric route of administration The latter authors believe, however, that fructose is not very useful therapeutically owing to its fairly extensive conversion to glucose. This would seem to be especially true in the case of oral administration. Respecting therapy of acidosis, the consensus is emerging (3) that fructose has little if any more to offer than glucose accompanied by somewhat large doses of insulin. Further confirmation of the difference in metabolism of these two sugars is provided by Craig *et al* (3a), who find that fasting or a carboydrate-free diet for two days decreases the rate of removal from the blood of intravenously administered glucose, but not fructose

Lipides—The tendency toward hyperlipemia in patients with uncontrolled diabetes has been recognized for years (4) This increase in serum lipides is attributable chiefly to the triglycerides, the other fractions, including cholesterol, being less consistently involved (5).

The general parallelism, with some individual exceptions, between levels of blood lipides and blood sugar in diabetic patients was noted by Gray (6) in 1924 and confirmed by Hirsch *et al* (7), who measured esterified fatty acids The amounts of these substances in the blood rose significantly higher after a fat meal when diabetes was poorly controlled than when it was well controlled. A positive correlation between levels of β-lipoprotein and blood sugar has been described in diabetic children (8). Obviously, these studies carry possible implications for the prevalence of atherosclerosis in diabetes.

Dole (9) and Gordon (10) have called attention to a hitherto neglected component of the blood lipides the behavior of which is also closely related to glucose metabolism—the nonesterified fatty acids (NEFA) While these

[1] Review of the literature was terminated with the June, 1958 issue of the journals to which reference is made

[2] The following abbreviations will be used· A-V (arterio-venous), DPN (diphosphopyridine nucleotide), GH (growth hormone), NEFA (nonesterified fatty acids); TCA (trichloroacetic acid), TPNH (triphosphopyridine nucleotide, reduced)

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alloxan diabetic rats there was also free equilibration of C^{14} glucose between plasma and liver water, and fructose, mannose, galactose, sorbitol, mannitol, glycerol, and α-methyl glucopytose, in addition to glucose, entered liver cells. The free permeability of such cells to glucose and other small carbohydrates suggests to the authors that the action of insulin in liver is not to increase the penetrability of the cell membrane, as is the case in muscle, but to alter intracellular enzyme functions.

In alloxan diabetic rat livers, as compared with nondiabetic, Mehler *et al.* (18, 19) have found greatly increased concentrations of an enzyme, picolinic carboxylase, which has no apparent relation to carbohydrate metabolism but forms picolinic acid from an oxidation product of 3-hydroxyanthranylic acid. Levels of this enzyme revert to normal slowly with insulin given *in vivo*.

Insulin

Insulin action.—Stadie (20), having critically analyzed the literature, including important contributions from his own laboratory, has proposed a "unified" concept of insulin action which is summarized as follows:

TABLE I

A Unified Concept of Insulin Action*

Tissue	Mechanism of Action	Site of Action	Chief Metabolic Effects
Muscle	combination of insulin with muscle	cell surfaces (immediate)	glucose transport and its sequelae
Liver	adaption	enzyme systems, contrapituitary (needs time)	glucose oxidation, fatty acid synthesis, oxidative phosphorylation
Adipose	adaption	enzyme systems	glucose oxidation, fatty acid synthesis
Brain, other	no demonstrable action	insufficient data	

* After Stadie (20).

Insulin in blood.—During the present decade several attempts to measure the concentration of circulating insulin have been made with results which range from 0.01 to 3.0 milliunits/cc. in normal "fasting" plasma (21 to 24), but which are considerably higher after the administration of glucose (24, 25). Further efforts in 1957–58 are summarized in Table II.

normally comprise only about 5 per cent of the total plasma fatty acids (11), they appear to have a rapid turnover rate and to be metabolically very active. Their levels are increased by fasting and epinephrine and are sharply decreased by the administration of glucose, certain amino acids, or insulin Studies of arterio-venous (A-V) differences indicate a net transport of NEFA from adipose tissue to myocardium, skeletal muscle, and abdominal viscera [and presumably utilization by these organs (12)]. The A-V differences are abolished by glucose and insulin. These observations are consistent with the hypotheses that the NEFA represent an important form of fat transport and that their concentration in the blood is increased when calories from nonfat sources, especially glucose, are not available. Also consistent with the latter hypothesis is the finding (13) that, in diabetic patients, levels of NEFA average 849 ± 287 μeq /L and in diabetics with ketosis, 1311 ± 466, compared with 572 ± 280 in normal individuals. Administration of glucose or glucagon is followed by a diminished and delayed fall of NEFA in diabetics as contrasted to nondiabetics. In diabetic acidosis insulin causes a decline of NEFA as dramatic as that of glucose. Experiments with labeled palmitic acid (14) indicate that insulin acts to inhibit the release of NEFA from the fat depots, not to increase their removal from the blood. Thus, it may be by the shutting off of the extravagant supply of fatty acids from the depots, consequent upon the resumption of glucose utilization, that insulin mitigates acidosis.

The impaired ability of the diabetic organism to synthesize fat was explored by Siperstein & Fagan (15, 15a) with results of considerable importance. In liver homogenates from normal rats, it was found that stimulation of glycolysis via the Embden-Meyerhof pathway by the addition of diphosphopyridine nucleotide (DPN) gave little or no increase in fatty acid or cholesterol synthesis from acetate C^{14} compared with controls, whereas stimulation of glycolysis via the hexose-monophosphate shunt by the addition of triphosphopyridine nucleotide (TPN) gave a 30- to 100-fold increase. In diabetic rat liver homogenates, DPN likewise resulted in little or no increase in fat synthesis, but TPN produced a 100- to 700-fold increase. Thus, the dependence of fat synthesis on glycolysis seems attributable to that part of glucose breakdown which proceeds by the hexose-monophosphate route. Since this shunt is activated by TPN (actually TPNH), it is concluded that the diabetic defect in lipogenesis is probably due to deficiency of this enzyme.

Liver

The fact that at least one function of insulin is to facilitate the entry of glucose into the cells of muscle, has been widely accepted since its demonstration by Levine and his co-workers (16). Cahill *et al.* (17) now report studies of the penetration of glucose into liver Using intravascular catheters, they have found that in normal dogs C^{14} glucose was freely distributed in total liver water, and that its concentration there was equal to that found in plasma water, whether the liver was taking up or releasing glucose. In

injected hormone in blood and tissues. The radioactivity in the trichloroacetic acid (TCA) precipitate of plasma of subjects or animals so treated was assumed, on the basis of some evidence, to be a measure of undegraded insulin as contrasted with degraded insulin whose radioactivity appeared in the supernate. In healthy human subjects the TCA-precipitable radioactivity (insulin I^{131}) disappeared from the plasma quickly, only 7.7 per cent remaining 60 min. after injection, whereas the majority of diabetic patients showed a much slower disappearance (37), owing presumably, as further investigations showed (31, 37), to the formation of insulin-binding antibodies by patients who had been chronically treated with insulin. Fifteen minutes after injection of insulin I^{131} only very small amounts of TCA-precipitable radioactivity had been excreted in urine; the largest amounts were found in liver and especially in the convoluted tubules of the kidney (rats) (36, 38) Nephrectomy retarded the rate of insulin I^{131} degradation (39, 40). What relationship these tissue phenomena have to Mirsky's "insulinase" (41) is presently unclear.

The assumption made in the foregoing studies, that the TCA-precipitable insulin I^{131} in plasma represents unaltered and fully potent insulin, was later questioned by its proponents (37) It has been thrown in further doubt by the work of Berson *et al.* (31), who have found in electrophoretic analyses that from 2 to 25 per cent of the total radioactivity of insulin I^{131} in plasma migrates with the globulin fraction and hence has undergone change of unknown nature These observations have been confirmed by Scott's group (42), who have also shown, in studies employing the glucose uptake of the rat diaphragm, that the labeling of insulin with I^{131} interferes measurably with its biologic activity.

Thus, it is apparent that the use of insulin I^{131} for the study of the metabolism of insulin has certain pitfalls which are now being recognized Nevertheless, this method has sufficient validity to have produced much new and valuable information on the localization and fate of the hormone in tissues and on its binding by serum proteins These findings may prove to have a bearing on problems such as insulin requirement, insulin resistance, and labile diabetes, among others (31, 37).

Glucagon

The action of glucagon in stimulating glucose release from the liver has been studied by Shoemaker & Van Itallie (43), using catheters in the splenic artery and portal and hepatic veins of unanesthetized normal dogs Glucagon given intravenously (site unspecified in the preliminary report) increased hepatic vein glucose concentration by 58 mg./100 cc., portal-hepatic vein glucose gradient by 18 mg /100 cc , hepatic blood flow by 710 cc /min , and hepatic glucose output by 304 mg /min Epinephrine given under the conditions of the experiments produced little glycolysis, but did yield a marked increase in hepatic vein potassium Makman *et al.* (44), by a fractionation procedure which gave 71 to 88 per cent recovery of glucagon added to blood

TABLE II

MEASUREMENTS OF CIRCULATING INSULINLIKE MATERIAL

Author	Normal human plasma or serum insulin, milliunits/cc.	Method and conditions
Renold *et al.* (26)	<0.2	glucose uptake of rat diaphragm, undiluted plasma, fasting subjects?
Baird & Bornstein (27)	1–2	glucose uptake of rat diaphragm; plasma from which insulin "antagonists" are chemically separated; fasting subjects
Beigelman & Antoniades (28)	0.75–1.4	blood sugar change in hypophysectomized, alloxanized rat after dextrin feeding; "protein globulin precipitate fraction" of pooled normal plasma
Beigelman & Antoniades (28)	0.25–1 0	glucose uptake of rat epididymal fat pad; pooled normal plasma diluted 1:2 to 1:10
Martin, Renold & Dagenais (29)	0 5–3 5	oxidation of glucose-1-C^{14} to $C^{14}O_2$ by rat epididymal fat pad, undiluted plasma; fasting subjects (increased after glucose feeding)

Although progress is being made, the available methods are still too complicated for general use and their sensitivity and reliability leave something to be desired.

Part of the difficulty in such measurements is the presence, even in normal blood, of factors that inhibit, mask, or antagonize the action of insulin. The nature of these substances is not known precisely. Their effects can be minimized by dilution of the plasma or serum (22, 23, 25, 28, 30) or their removal by fractionation (27, 28) before testing. The binding of insulin by serum globulins has been shown to occur to a far greater extent in diabetic and schizophrenic patients who have had repeated injections of the hormone than in normal subjects or noninsulin-treated patients (31, 32, 33) An antagonist to insulin from both animal and human sources has been demonstrated by Field & co-workers (34, 35) in the sera of some patients in diabetic acidosis, and its presence may be independent of previous insulin therapy.

Elgee, Williams & Lee (36) have used insulin I^{131} to study the fate of the

Lundbaek (50) has reviewed the clinical aspects of diabetic vascular disease and added the latest compilation of his own experience with long-term diabetes. He concludes, in company with many predecessors, that duration of diabetes is the most important single factor in the development of these complications.

Sigroth (51), measuring the skin temperature of the fingers of normal and diabetic subjects after the hands had been immersed, first in a cold and then in a warm bath, found a subnormal rise in 53 of 91 diabetics. This impaired response, indicating an abnormality of the smaller vessels, was correlated inversely with the age at onset of diabetes and directly with poor control of glycosuria and presence of renal and retinal disease, but not with age, sex, blood pressure, basal metabolism, or frequency of insulin reactions

Ditzel has studied the conjunctival vessels of diabetic patients during life for several years He and his colleagues (52) have found a marked lability in the caliber of the conjunctival venules in 7 of 10 young diabetics, but in none of 15 normal subjects observed over a period of hours. These changes were most marked in the morning, but were not correlated with blood sugar levels or other factors In another report, in which 60 diabetics with and without retinopathy and nephropathy were studied, Ditzel *et al.* (53) state that there was a significant relationship between abnormal conjunctival vascular patterns and the extent of small blood vessel degeneration, regardless of the duration of diabetes These interesting results will be difficult for others to confirm because of the long practice needed to acquire the requisite skill in observation.

No new light has been shed on the cause of diabetic vascular disease. Earlier work (54, 55) tending to implicate elevated levels of mucopolysaccharides in retinopathy and nephropathy established only an association, not an etiologic relationship, with these conditions

The failure to pin responsibility on any of the known biochemical abnormalities of diabetes, except possibly hyperlipemia in some cases with atherosclerosis, has led to the conjecture that constitutional factors inherited along with the diabetic trait may be involved (56) However, individual case reports continue to appear in which extirpation or gross disease of the pancrease resulting in diabetes, in the absence of any known familial tendency toward the disease, is followed by specific vascular lesions (56) The latest [Burton *et al* (57)] concerns a patient with a negative family history who developed typical, although mild, diabetic retinopathy three years after total pancreatectomy. Apparently, then, something connected with the diabetic state itself is capable of damaging blood vessels Attempts to find significant vascular lesions in the experimental diabetes of animals have met with both success (58 to 61) and failure (62, 63). Species differences are probably important.

Some of the evidence advanced by Becker *et al.* (64) for hyperactivity of the adrenal cortex in diabetic retinopathy has been denied by Rifkin and his co-workers (65), who were unable to find differences in urinary steroid

or plasma and presumably removed glucagon inhibitors, and using liver homogenates as a test system, found an average of 7 μgm./100 cc. of glucagonlike material in either the peripheral and pancreatic vein blood of dogs, or both, and in peripheral venous blood of human subjects. It is probable that the substance found in the general circulation could have been glucagon which originated in the pancreas; this assumption was suggested by the recovery in femoral vein blood of crystalline glucagon injected into the portal vein of dogs.

If glucagon does indeed reach the greater circulation, one of its functions might be to influence the peripheral utilization of glucose. Tomizawa & Hyde (45), after pointing out that previous work on this problem has led to diametrically opposite conclusions, describe their own experiments, which showed that following intravenous injection of insulin-free, crystalline glucagon in dogs, A-V blood sugar differences after the hyperglycemic peak were the same as those following glucose injection. This result is interpreted to indicate that glucagon does not affect the peripheral disposal of glucose. However, a general metabolic effect is suggested by the work of Davidson & Salter (46), who found that the subcutaneous injection of 1 mg of crystalline glucagon gave a 35 per cent increase in oxygen consumption in normal, fed rats and a 25 per cent increase in fasted rats, the rise being maximal at 1 hr. and diminishing over 7 hr. The effect was not caused by hyperglycemia *per se*, for administration of glucose produced only a 4 per cent increase. The effect of glucagon was prevented by thyroidectomy or adrenalectomy and augmented by administration of epinephrine and especially by pretreatment of adrenalectomized rats with cortisone. Clearly, these phenomena need further investigation.

Sirek *et al.* (47) have reported that blood from the pancreaticoduodenal vein of donor dogs treated with purified growth hormone (GH), when injected into depancreatized dogs, increases blood sugar, but jugular vein blood from donor dogs does not. However, GH also gives rise to a hyperglycemic substance in the "central" (portal?) vein blood of even a depancreatized dog, so that the pancreas cannot be its only source.

Ezrin *et al.* (48) have described the effects of intravenous administration of glucagon for 10 hr. daily, for periods up to four days, to patients with active rheumatoid arthritis. The disease was ameliorated and, in addition to hyperglycemia, increased azoturia, markedly decreased creatinuria, and the appearance of ketosis were observed. This work confirms previous studies (48a, 48b) in demonstrating increased urinary nitrogen excretion following the administration of glucagon, and suggests that at least some of the hyperglycemic effect is attributable to gluconeogenesis from protein.

Clinical Diabetes

Vascular complications.—For the two-year period ending in December, 1957, 77.7 per cent of the deaths among Joslin's (49) patients were caused by cardiovascular-renal disorders.

of routine management over a period of days or weeks Maintenance doses of tolbutamide should not exceed 2 gm daily. Side effects are neither very common nor very severe. While at first there seemed to be no point in using both tolbutamide and insulin, there are now reports which indicate that combined therapy reduces the blood sugar fluctuations of labile diabetes (86, 87, 88), and is helpful in combating insulin resistance (89, 90).

Mechanism of action —The use of a new remedy for a life-long disease will always be attended by some uneasiness until its mechanism of action is known. Despite three years of intensive investigation, this goal has not been achieved for the sulfonylureas.

The only point on which there is agreement is that when these drugs lower the blood sugar there is also a diminished production or release of hepatic glucose. Conceivably, this could result either from a direct effect on the liver or from the release from the pancreas of extra insulin which, in turn, acts to reduce hepatic glucose output. Even if the effect is primarily on liver, it must take place in cells which are conditioned by a certain minimum amount of insulin, whether extra or residual, for insulin is essential to any action of the drugs The liver, however, is not essential, for a hypoglycemic response can still be elicited in hepatectomized animals (90a, 90b, 102). This is not to say that the liver does not participate in the reaction when it is present

The most popular hypothesis is that the sulfonylureas stimulate the release of pancreatic insulin. Recent, as well as earlier, investigations have yielded evidence both for (80, 81, 82, 91 to 96a) and against (80, 81, 82, 97 to 111) this idea A few examples will illustrate the present state of confusion· First, von Holt *et al.* (91) have demonstrated increased glycogen deposition in the rat diaphragm when incubated with plasma taken from rats given a single dose of carbutamide but not with plasma from rats treated daily with the drug for three months Renold *et al.* (103), using the glucose uptake of the rat diaphragm, were unable to demonstrate such insulinlike activity in plasma from normal human subjects after a rapid intravenous infusion of tolbutamide (37.5 mg /kg). Goetz & Egdahl (96a), on the other hand, employing the hypoglycemic response of fasted mice, found insulinlike activity (controls showed none) in the pancreatic vein blood of dogs following peripheral intravenous administration of tolbutamide (50 mg /kg). Secondly, the totally depancreatized dog receiving suboptimal amounts of insulin responds to daily doses of the sulfonylureas with a fall in blood and urinary glucose (97, 98, 99, 101, 102), but this is not true of depancreatized patients (112 to 115a) or juvenile diabetics (116 to 122), the latter also presumably lacking endogenous insulin Third, if the pancreas is stimulated to release more insulin, many of the known effects of insulin in addition to hypoglycemia should be detectable Among these, the following have been both claimed and denied (80, 81, 82, 93, 94, 96, 103, 104, 105, 108 to 111, 123 to 127): increased blood lactate and pyruvate, respiratory quotient, positive arteriovenous blood sugar difference and glucose uptake

levels and response to ACTH in patients with and without retinopathy. Another contention of the Hopkins group (64, 66), that vitamin B_{12} metabolism is abnormal in diabetic retinopathy, has been refuted by Field *et al.* (67). Reports of adrenalectomy (68 to 71) and hypophysectomy (72, 73) for

... have been difficult to evaluate because of

possibility of spontaneous

...nt. These factors, plus some freely admitted equivocal results and frank failures, make it doubtful that *such operations will be of practical value.*

Kinsell et al. (74) report that the feeding of large amounts of *linoleic* acid, an unsaturated, "essential" fatty acid, leads to regression of symptoms and signs in patients with partially occlusive peripheral vascular disease, and to arrested progression of retinal and renal disease in diabetes. The mechanism by which such improvement occurs is obscure, despite the well-known effect of dietary polyunsaturated (vegetable) fats in lowering serum cholesterol levels, discovered by Kinsell (75).

Acidosis—Aoyama & Kolff (76) describe the successful use of the artificial kidney in a case of severe and prolonged diabetic acidosis with anuria and azotemia.

Pregnancy—Hoet (77) believes, on the basis of evidence, that the accidents of pregnancy in women with abnormal glucose tolerance but without frank diabetes can be reduced by treatment with insulin. In a long-term, comprehensive, and well-controlled study still in progress and designed to test Hoet's hypothesis, Wilkerson & Remein (78) report that among 192 live births, three times as many overweight infants (9 lb. or more) were born to women with abnormal carbohydrate tolerance from whom treatment was withheld, as were born to women with abnormal tolerance who were treated with insulin, or to a sample of women with normal tolerance A study with similar implications but a somewhat different approach has been reported by Carrington *et al.* (79).

Oral Hypoglycemic Agents

The literature dealing with the oral hypoglycemic agents has reached staggering proportions and cannot be fully covered here For detailed developments up to the past year, the reader is referred to certain symposia (80, 81, 82) which will be drawn upon in the ensuing paragraphs, often without specific reference.

Clinical aspects.—There is general agreement that the sulfonylurea compounds cannot replace insulin in severe or well-established juvenile diabetes or in diabetic acidosis and other emergencies They do not act in the complete absence of insulin. Among the milder diabetics who have required small to moderate doses of insulin and who presumably can still manufacture some of their own, injected insulin can be replaced by oral drugs in 50 to 60 per cent (83, 84, 85). Some physicians (85, 86) use special tests to determine responsiveness, but these are not wholly reliable, and many prefer the test

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by the rat diaphragm, and decreased nitrogen excretion, serum lipides, ketone bodies, and serum phosphorus levels after glucose loading. No doubt these differences in experimental results are related to differences in species, condition of animals (anesthesia), size and chronicity of dosage, timing and source of samples, and other variables. It is likely to be some time before they are reconciled.

The past year has seen the introduction of two new oral hypoglycemic agents. One, chlorpropamide (128 to 131), is another sulfur-containing agent which is effective in smaller doses than tolbutamide, but more toxic The other is phenylethyldiguanide (DBI, PEDG), a totally different kind of compound (132 to 138), whose action seems to depend upon the promotion of anaerobic glycolysis; its use in man is accompanied by a high incidence of gastrointestinal disturbances.

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ENDOCRINOLOGY (REPRODUCTION)[1]

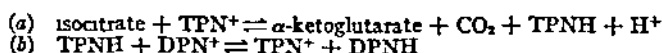
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The limitations imposed by time and space prohibit writing which even approximates a thorough review of recent advances in the vast field of endocrinology. Arbitrary restrictions were necessary. Accordingly, this article will deal predominantly with the gonads and the actions of their internal secretions. Even within this narrowed field no all-inclusive systematic survey of recent advances has been prepared. Instead, nine major subjects were chosen for review and comment. It was hoped that this concentration on sex and reproduction would not be distasteful or foreign to the interests of specialists in internal medicine. By virtue of the same restrictions, recent authors of endocrine reviews in the *Annual Review of Medicine* have dealt lightly with the ovaries and testes

MECHANISM OF ACTION OF ESTROGEN

In two recent communications, Talalay & Williams-Ashman (1, 2) have reported on studies which take an exciting step toward an understanding of the basic biochemical mechanisms by which estradiol and perhaps other steroid hormones exert their influence. Villee & Hagerman (3, 4, 5) had shown that the reduction of deoxyribonucleic acid in a reaction in which isocitrate was converted to α-ketoglutarate was catalyzed by an enzyme present in human placental homogenates, and that this reaction could be accelerated by estradiol-17β and several other steroid substances with hormonal activity. The enzyme was found to be present in the cell-free supernatant of these placental extracts Villee interpreted these results as indicating that estradiol stimulated isocitric dehydrogenase and suggested that the hormone converted an inactive to an active form of isocitric dehydrogenase, presumably by forming an enzyme-steroid complex

Talalay & Williams-Ashman readily confirmed the initial observations of Villee's group, but then showed that the apparent stimulation of a DPN-linked isocitric dehydrogenase could be accounted for by a coupling of the triphosphopyridine nucleotide-specific isocitric dehydrogenase enzyme of the placenta and a transhydrogenating system as follows:



(a) isocitrate $+ TPN^+ \rightleftharpoons$ α-ketoglutarate $+ CO_2 + TPNH + H^+$
(b) $TPNH + DPN^+ \rightleftharpoons TPN^+ + DPNH$



sum isocitrate $+ DPN \rightleftharpoons$ α-ketoglutarate $+ CO_2 + DPNH + H$

It is the second step in this system (*b*), the transhydrogenation, which was activated by minute amounts of estradiol ($10^{-7}M$) In this reaction which involved stoichiometric quantities of the nucleotides and catalytic concen-

[1] The survey of literature pertaining to this review was completed September, 1958.

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steroid might be useful in hastening recovery from debilitated states has been explored more or less continuously by a number of different workers ever since the initial suggestion by Kenyon in 1942 (15).

Testosterone, or one of its related anabolic steroids, has induced nitrogen retention and has been thought to be useful therapeutically in a variety of clinical states in which there has been substantial loss of tissue protein (16). It should be appreciated that although demonstration of anabolism in the presence of severe illness can be achieved, satisfactory evidence of clinical benefit is much more difficult to develop. More or less empirically, treatment with an anabolic steroid might be used in those debilitated patients in whom the wasting process was not arrested or reversed because a nutritional inadequacy persisted That testosterone may be anabolic under very unfavorable nutritional conditions was indicated by Kochakian (17) who showed that in fasted guinea pigs the growth of some skeletal muscles and accessory sex glands was enhanced by the androgen. Testosterone was also anabolic in Cushing's syndrome (14) and induced hypercorticism so that it might be a useful adjunct in some patients with collagen diseases, ulcerative colitis, etc., who have been treated with large amounts of corticoids or corticotropin.

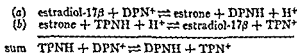
In patients who are recovering from severe illnesses and in many individuals with induced hypercorticism, the food intake may be enormous. A large surfeit of calories with an abundance of good dietary protein will spare tissue protein most effectively, and also favor the rapid restitution of the body's protein stores in depleted patients. Whether testosterone could offer much therapeutically in these circumstances is highly problematical.

Synthetic Anabolic Agents

In females and prepubertal boys to whom testosterone may be given for anabolic or growth promoting purposes, the virlizing influence of the hormone is undesirable. Accordingly, a considerable effort has been made to synthesize a steroid which is as anabolic as testosterone but is much less androgenic. For biological screening purposes the growth induced in the levator ani muscles of castrated rats has been used as an index of myotrophic activity which has been equated with general anabolism; and the growth of accessory sex glands has served as the indicator of androgenicity (16, 18). A number of steroids have been tested in this manner and those which had a greater anabolic/androgenic ratio than testosterone were given clinical trials. With some compounds there has been a satisfactory correlation with estimates of androgenic and anabolic influence in man, but this has not always been the case. Gordon, who helped develop the procedure, has pointed to its relative crudity and to defects in its execution in some hands (16). Since the search is for steroids with specific activities in man, there can be no substitute for the time-consuming human studies.

Huggins & Jensen (19) and Sydnor (20) have employed the growth of the uterus and vaginal epithelium in hypophysectomized female rats as an indicator of the growth promoting potential of steroids With their prepara-

trations of the steroids, the hormone was alternately oxidized and reduced in the process of transferring hydrogen and has accordingly been regarded by Talalay & Williams-Ashman as a co enzyme.



$$(a)\quad \text{estradiol-17}\beta + \text{DPN}^+ \rightleftharpoons \text{estrone} + \text{DPNH} + \text{H}^+$$
$$(b)\quad \text{estrone} + \text{TPNH} + \text{H}^+ \rightleftharpoons \text{estradiol-17}\beta + \text{TPN}^+$$
$$\text{sum}\quad \text{TPNH} + \text{DPN}^+ \rightleftharpoons \text{DPNH} + \text{TPN}^+$$

The placental dehydrogenase activity could not be separated from the transhydrogenating enzyme despite a hundredfold concentration. This fact, as well as other experiments, led to the conclusion that the same enzyme catalyzed both types of reactions. Thus, with stoichiometric quantities of the pyridine nucleotides, minute quantities of estradiol acted as a co-enzyme in transhydrogenation. With stoichiometric amounts of estradiol the enzyme functioned as an hydroxysteroid dehydrogenase. It was suggested that all hydroxysteroid dehydrogenases, a number of which have been isolated from various mammalian tissues, could function similarly as transhydrogenating enzymes. This has already been demonstrated with respect to rat liver 3 α-hydroxy dehydrogenase (6).

In their speculations, Talalay & Williams-Ashman have suggested that at least some of the biochemical consequences of estradiol-17β as well as other steroid hormones may stem from this transhydrogenation of pyridine nucleotides Hydroxysteroid dehydrogenases have an unusual ability to bind estradiol and other steroids (7), a fact which is probably related to the catalytic effect of estradiol in transhydrogenation. Dehydrogenases from various tissues may differ in their affinity for hormones and of course tissues undoubtedly differ in their hydroxysteroid dehydrogenase content, both quantitatively and in terms of the specificity of the enzyme. Such differences were suggested as a possible basis for the specificity of hormone action as well as an explanation for the well-known overlap in the actions of steroid hormones The probability that prostatic tissue binds testosterone about 2½ times as effectively as muscle (8) is consistent with this view. According to the hypothesis of Talalay & Williams-Ashman, the steroid hormones could enhance energy capture from the oxidation of the reduced nucleotides, and also participate in biosynthetic reactions of responsive tissues by means of this catalysis of the transhydrogenation of pyridine nucleotides.

METABOLIC INFLUENCE OF ANDROGENS AND ESTROGENS

An appreciation of the general metabolic influence of the sex hormones probably dates from the demonstration by Kochakian & Murlin (9) in dogs and Kenyon and his associates (10) in man that testosterone was a potent anabolic agent. Shortly after this estradiol was also shown to be anabolic, although probably somewhat less so than testosterone (11, 12). Following this initial work, Kenyon (13), Albright *et al.* (14) and, subse-

pausal osteoporotics, therapy with estradiol benzoate and other estrogens has reversed negative calcium balances and induced positive balances of as much as about 200 mg. per day for 150 days or longer. Lengthier balance studies have not been reported. Since about 99 per cent of the 1200 gm. of calcium in the average human body is in bone (33), Albright's assumption that calcium was deposited in rarified bones would seem justified on quantitative grounds alone.

Henneman & Wallach (34) have recently completed a 9 to 20 year follow-up study of 200 osteoporotics from Albright's clinic. The postmenopausal osteoporotics had been treated with estrogens, and the senile osteoporosis in men with androgen. They reported that in all of the patients the progress of the osteoporosis was arrested as indicated by an abrupt cessation in the shrinkage in height, the lack of unfavorable progression radiologically, and symptomatic improvement. They were unable to demonstrate recalcification of the bones radiologically, but this is admittedly an insensitive technique. Other members of the Albright school support these findings (35, 36). Reifenstein (36) and some others favor the combined estrogen and androgen treatment of osteoporosis. The advantages of this combination over the use of one or the other hormone in the appropriate sex appear highly questionable except perhaps in some unusual situation.

There remain some skeptics, and it is too bad that serial biopsy studies of bone have never been carried out during treatment of postmenopausal or senile osteoporosis. Spectacular recalcification of the osteoporosis of Cushing's syndrome has been easily visualized roentgenologically (35, 47). The inability to secure such proof in these other osteoporotics would accordingly suggest that, at most, estrogen and androgen were only partially able to correct the defect. If this is true, postmenopausal osteoporosis and senile osteoporosis are probably not the result of a deficiency of the sex hormones as has often been implied, but rather some bone tissue defect which may be accentuated by the lack of gonadal secretions.

METABOLIC EFFECTS OF PROGESTERONE

Influence on Protein Metabolism

Progesterone's influence on protein metabolism is quite the opposite of that of testosterone and estradiol. Despite the fact that it is growth promoting in the endometrium, breast parenchyma, and sebaceous glands (37), the net effect of physiologic quantities of the hormone in man is moderately catabolic. This was initially demonstrated in an isolated experiment by Abels & Dobriner (38), but now the enhanced metabolism of protein has been induced by intramuscularly administered progesterone in a variety of circumstances in both men and women (39, 40). Its elicitation did not require the presence of estrogen, adrenocortical hormones, the thyroid gland, or the hypophysis (41). From the qualitative point of view the catabolic process can be distinguished from that induced by an excessive secretion of thyroid hormones or adrenocorticoids. With both the latter secretions, the

tion they have tested a number of compounds and have reached rather definite conclusions concerning the participation of functional groups of the steroid nucleus in anabolic processes. It appears that neither the ketone nor the hydroxyl group at C_3 was important. Whether or not there was unsaturation in ring A also seemed inconsequential. The critical function as shown by their studies was the 17β-hydroxyl group (like that in testosterone). The 17-ketosteroids were either completely inactive or elicited only a slight growth response. In general, the essential nature of the 17β-hydroxyl group for growth promoting activity has been borne out in studies in man (see below). Δ^4-Androstenedione-3,17, which was mildly anabolic in two normal women (21) as it was in castrate dogs (22), is a notable exception. Nevertheless, the primacy of the 17β-hydroxyl group as well as this assay method should be kept in mind in the search for new anabolic steroids.

Gordan (16) has referred to several compounds which have never passed the hopeful stage. Until recently, methyl androstenediol had been the only anabolic steroid with somewhat less androgenicity than testosterone which had achieved any acceptance. Another, the phenyl-propionic acid ester of 19-nortestosterone (23) seemed hopeful from the levator ani test, but has not received clinical trial. Two newer compounds seem at the moment to come closer to the ideal. Both are 19-nor derivatives of testosterone, and both are very potent progestins (see synthetic progestational compounds below).

Only 17α-ethyl-19-nortestosterone has received extensive clinical trials In the guinea pig it was only about one-fourth as androgenic as testosterone propionate although approximating its anabolic action (24) In prepubertal boys it was weakly androgenic (25) Balance studies from a number of laboratories have demonstrated significant nitrogen retention under both favorable and unfavorable conditions (26, 27), its anabolic influence approximating that of testosterone propionate whether it was given parenterally or by mouth (28).

The second compound, 17α-ethinyl-19-nortestosterone has little androgenic activity in the castrated rat, and moderate growth promoting influence on the levator ani (29, 30) Early lots of the material contained estrogenic contamination, but even the more highly purified batches have had slight estrogenic activity, suggesting that this might be a characteristic of the steroid itself Estimates of androgenicity in man are wanting, but there is no doubt that it is anabolic (28, 31) Since both of these compounds are powerful progestins the possibility of withdrawal bleeding in women with active ovaries must be kept in mind when they are being used for their anabolic activity.

Osteoporosis

Estrogen and androgen have been widely used in the treatment of postmenopausal and senile osteoporosis since Albright's initial suggestion and reports (32). Both hormones have induced positive calcium balances although estrogen is usually more effective than testosterone. In some postmeno-

subjects as well as the sodium retention which followed discontinuance of progesterone in these people was the result of an adrenal response to the circulating progesterone or the loss of body sodium, or both An explanation for premenstrual edema could lie in part in a minor disturbance of such an inter-relationship of progesterone and aldosterone secretion during the luteal phase of the menstrual cycle. The therapeutic value of an aldosterone inhibitor in patients with salt and water retention remains to be determined.

Two unusual compounds, 3(3-oxo-17β-hydroxy-4-androsten-17α-yl) propionic acid γ-lactone and its 19-nor analogue, have been tested in rats by Kagawa and his associates (48) and found to inhibit the sodium retaining influence of aldosterone much as does progesterone. Liddle (49) elicited a similar response with these two drugs in man. Quantitative studies in rats indicated that the drugs were more potent than progesterone in their aldosterone-inhibiting capacity All three appeared to follow the law of mass action in this reaction in rats, and in man there were indications of a quantitative relationship in the inhibition of aldosterone by progesterone (45).

Structural Requirements for Metabolic Influence of Progesterone

As a result of the comparison of the metabolic effects of several progestational compounds (see later sections) it has been possible to reach some tentative conclusions concerning the key chemical requirements for aldosterone inhibition and the catabolic influence of the hormone (28) All of the steroids tested were 3-ketones with a double bond between carbons 4 and 5 of the A ring. The principal points of variance were the C-17 substituents and their spatial configuration. The angular methyl group between rings A and B was missing in some steroids (19-nor compounds), but this variation did not appear to have a qualitative influence on the metabolic processes measured.

An enhancement of the rate of protein catabolism was induced only by steroids on which the two carbon side-chain attached at C-17 was beta-oriented like progesterone and the adrenal hormones Active progestational agents with the side chain in the alpha position were either anabolic or questionably so. The 20-ketone was not critical; 20α-hydroxy progesterone was catabolic, but the 20β-hydroxy isomer was metabolically inert (50)

Much less can be said about the key characteristics for the elicitation of the natriuretic response to progesterone (aldosterone and deoxycorticosterone inhibition). Of all the compounds studied only progesterone and the unusual substances described by Kagawa *et al.* (48) possessed this property. The 17α-hydroxy derivatives of progesterone, the 20-hydroxy progesterones, and the progestins with alpha-oriented side chain had no such action Presumably the competitive inhibition must require some close stereochemical resemblance to deoxycorticosterone and aldosterone.

NATURALLY OCCURRING PROGESTATIONAL AGENTS

Recent methodological improvements have made it possible to estimate the concentration of progesterone in placentas, corpora lutea, fat tissue,

enhanced catabolism of protein (increased urinary nitrogen output) was accompanied by distinct elevations in plasma and urinary amino acid (42). However, when progesterone was given, plasma and urinary amino acid levels were either slightly suppressed or unaffected.

The meaning and the significance of this rather surprising influence of physiologic quantities of progesterone is obscure. The rise in urinary nitrogen excretion has been elicited by as little as 12.5 mg. of progesterone per day, an amount which, judging by pregnanediol excretion studies, approximates the quantity secreted by the normal woman during the luteal phase of the menstrual cycle. It was usually maximal in intensity at a dosage of 50 mg. per day which is about the amount secreted daily during early pregnancy (43). The large amounts of progesterone which are continuously secreted during pregnancy suggest that this influence on protein metabolism may be of the greatest physiologic importance during gestation. Dewar (44) has shown that there is normally a significant gain in the extrauterine weight of pregnant mice which seems to be related solely to the presence of progesterone. In part, this was fluid retention. Neither estrogen nor the adrenal cortex appeared to be responsible for this phenomenon. A similar gain in weight was induced by progesterone in nonpregnant animals, and an increased food intake was observed during this progesterone-induced period of weight gain. This observation could well be related in some way to the enhanced protein catabolism noted above in man.

Effect on Sodium Excretion

In normal women and men, progesterone also exerts a natriuretic and chloriuretic influence. This effect was also observed over a dosage range approximating the rates of progesterone secretion in pregnant and nonpregnant states (12.5 to 300 mg per day). The sodium loss induced by the smallest dosages was rather slight but with 200 to 330 mg. daily, as much as 396 m.eq. of sodium was dissipated in eight days (43). This natriuretic influence of progesterone was more intense in fully treated Addisonians than in normal subjects, but when given to adrenal-deficient patients who were not being treated with a salt retaining corticoid, sodium excretion was not affected (39). From this it was deduced that the natriuretic influence of progesterone was the result of a competitive inhibition of the action of salt retaining corticoids in the kidney tubules. The inhibition of both deoxycorticosterone and aldosterone has been demonstrated in subjects without functioning adrenal glands (39, 45). Presumably the salt loss induced in persons with intact adrenals is based upon a similar inhibition of endogenous aldosterone.

This discovery should, like the catabolic potential of progesterone, find its place in the complex physiology and pathophysiology of pregnancy and the normal menstrual cycle The increased excretion of aldosterone in the urine during pregnancy (46) may well reflect its enhanced secretion in response to the inhibitory influence of the immense quantity of progesterone secreted by the corpus luteum and the placenta. In the experiments reported it was suggested that the less intense natriuresis observed in normal

castrated woman. Replacement dosages would accordingly be substantial and, for lengthy courses of treatment, would require almost daily injections. The hormone was relatively inactive when given by mouth (59). The primary aims from the viewpoint of replacement have been to find steroids wither greater potency, oral effectiveness, and protracted action when given parenterally. New compounds which have been developed and tested clinically appear in three categories: (*a*) derivatives of 17α-hydroxyprogesterone; (*b*) derivatives of testosterone; (*c*) halogenated derivatives of progesterone.

In the first group the parent compound, 17α-hydroxyprogesterone, possesses very little progestational activity (60). It was therefore quite surprising to find that when the 17α-hydroxy group was esterified, compounds with remarkable progestational activity were developed. Not only were these esters more active progestationally than progesterone but the duration of their biological influence was considerably lengthened (61). At least one of these esters was also shown to be active when given orally (62). The transformation of biological activity brought about by simply esterifying 17α-hydroxyprogesterone has not been explained If the ester were hydrolyzed to the free 17α-hydroxyprogesterone, one would not anticipate enhanced activity for, as noted, it is a weak progestin If progesterone were the active material, enhanced pregnanediol excretion would be expected. Neither pregnanediol nor pregnanetriol, the urinary metabolite of 17α-hydroxyprogesterone, have been found in increased quantities after the administration of the esters of 17α-hydroxyprogesterone (63). The caproate has been tested extensively as a long acting progestational compound. Doses of 200 to 500 mg. have produced progestational and metabolic changes which lasted for at least two weeks (64, 65, 66). The clinical trials with 17α-acetoxyprogesterone have demonstrated that 75 to 100 mg per day by mouth would produce a "full" progestational endometrium (62).

Derivatives of Testosterone

All of the steroids in the second category have the beta-oriented, 17-hydroxyl group characteristic of testosterone. Instead of the beta-oriented side chain of progesterone, these compounds have an alpha-oriented, two carbon chain or a methyl group in the same position. All were active when given by mouth. Ethisterone or 17α-ethinyl testosterone is not new at all, but has been widely used as an oral progestin for many years. Depending on the end point used (full secretory endometrium, withdrawal bleeding, characteristic changes in vaginal epithelial cells), and probably also on the duration of dosage schedules it has been shown to be from about one-tenth to one-fifth as active orally as parenteral progesterone (56, 59). Norethisterone, 19-nor-17α-ethinyl testosterone, was five times as active as ethisterone in rabbits (67), and in man about twice as effective (56, 59). The enanthate ester of norethisterone given intramuscularly produced a long-acting, progestational effect and was about twice as active as the 17α-OH progesterone caproate and acetate (56). Other 19-nor derivatives of testosterone, 17α-

blood, etc., as well as to determine the total progestational activity of the tissue samples. The biologic assays have consistently pointed to the presence of a substantially larger amount of hormonal activity than could be accounted for by progesterone (51 to 55). Zander *et al.* (55) have been able to explain this discrepancy, at least partially. They have identified two compounds obtained from the placenta, ovaries, fat tissues, and probably blood, Δ^4-3-ketopregnene-20-α-ol and Δ^4-3-ketopregnene-20-β-ol, which are potent progestins as shown by two bio-assay procedures The 20α-hydroxy compound was one-sixth to one-third as active as progesterone in mice (Hooker-Forbes assay) and about the same in rabbits (Clauberg assay). The beta isomer was one-fifth to one-tenth as active as progesterone in rabbits but twice as potent as progesterone when tested in mice. Other investigators working independently have also found the 20-hydroxy progesterones in biological materials (55). Both isomers were isolated from human tissues after the administration of progesterone so that the authors were convinced that they were dealing with metabolic derivatives of progesterone rather than primary secretory products of the corpus luteum or placenta. It can be readily seen that 20α-hydroxy progesterone is an intermediate in the degradation of progesterone to its well-known urinary metabolite, pregnane-$3\alpha,20\alpha$-diol. The 20β isomer has not as yet been found in urine extracts.

Weid & Davis (56) have tested the 20-cyclopentylpropionates of these two compounds in estrogen-primed, castrated women and found them to be mildly to moderately progestational. Esterification could profoundly influence the biological activity as has been shown in other derivatives of progesterone (see below), so that modest activity of these esters in man does not necessarily accurately reflect the relative activities of the free alcohols Only the metabolic aspects of the free compounds have been studied in any detail. As noted in the foregoing section, Δ^4-3-ketopregnene-20α-ol produced a rise in basal body temperature and was catabolic like progesterone. The 20β-hydroxy derivative had neither of these activities, and neither of the steroids showed any indication of being an aldosterone inhibitor (50).

The fact that these two derivatives of progesterone are biologically active and circulate in blood strengthens the view that progesterone is the principal, if not the only, active progestin secreted in man. It is still quite possible, however, that other circulating progestins may be identified.

SYNTHETIC PROGESTATIONAL AGENTS

As in the case with androgens and estrogens, organic chemists and pharmacologists have devoted much effort to the development of progestational [illegible] the natural hormone.
[illegible] ılated on the basis of
[illegible] from 5 to 25 mg. per
day during the luteal phase of the menstrual cycle and from 25 to about 300 mg. daily during pregnancy. Weid & Davis (56) found that 20 mg. per day was required to induce "full" secretory endometrium in the estrogen-treated,

tional drugs have been tested in clinical situations in which the difficulties of evaluation have been immense, and the efficacy of progesterone itself has not been proven beyond a reasonable doubt.

CLINICAL APPLICATIONS OF PROGESTATIONAL COMPOUNDS

As indicated in the previous section, the use of progesterone and other progestational compounds therapeutically is in the early stages of evolution, but has been stimulated by the availability of the many new and interesting compounds If one disregards at this point the potential therapeutic value of anabolic 17β-hydroxy progestins (see section on metabolic effects of androgens and estrogens), one is left with four areas in which clinical investigation has indicated at least a potential usefulness of this group of progestins: (*a*) a test for ovarian function, (*b*) treatment of menstrual disturbances; (*c*) suppression of ovulation, (*d*) the preservation of pregnancies in habitual aborters

Test for Ovarian Function

For a number of years the injection of progestational quantities of progesterone has been employed as a specific functional test for estrogen secretion by the ovaries in patients with amenorrhea (84). It has been assumed that if bleeding followed progesterone withdrawal, it was from a secretory endometrium. Since the development of secretory changes requires estrogen priming, withdrawal bleeding indicates at least a basal level of estrogen secretion Any synthetic progestational agent could properly substitute for progesterone in this test providing it possessed no overlapping estrogenic activity. 17α-ethyl-19-nortestosterone and the esters of 17α-OH-progesterone would probably fulfill this requirement Norethynodrel and 17α-ethinyl-19-nortestosterone would not since both, as previously noted, are weakly estrogenic (85).

Treatment of Menstrual Disturbances

Perhaps the gynecologic disorder which has responded most uniformly to treatment with progestational steroids has been functional uterine bleeding. In this condition the endometrium is apparently subjected to continuous estrogen stimulation, and normal secretory changes do not evolve spontaneously. Treatment with a short course of progesterone or progesterone plus an estrogen in small quantity induced secretory changes in the endometrium followed by withdrawal bleeding and then usually a cessation of bleeding (medical curettage) (99, 100). The long-acting progestins like 17α-hydroxy progesterone caproate have performed as well as progesterone injections in this regard; and both norethynodrel and 19-nor-17α-ethinyl testosterone show exceptional promise. Bleeding has often stopped after the first few days of a short course of just 10 to 20 mg per day. One course with any of these steroids cannot be expected to prevent recurrences, but repeated cyclic courses of the progestins or progestin and estrogen have pre-

ethyl-19-nortestosterone, 17α-methyl-19-testosterone, 17α-ethinyl-5(10) estraene-17β-ol-3-one (norethynodrel) as well as a number of others with larger chain substituents in the 17α-position have been tested in rabbits and found to have progestational activity comparable with that of progesterone (30, 68 to 71). Quantitative comparisons with progesterone in man have not been completed with any of these, although all of those mentioned by name have been shown to be active oral progestins.

HALOGENATED STEROIDS

In the course of studying the various halogenated steroids developed by Fried (72) several were shown to have unusual progestational activity. The 11-keto and 11-β-hydroxy-9α-fluoro and bromo derivatives were progestational when given to rabbits parenterally or by mouth (73, 74). Wied & Davis (75) very carefully estimated the activity of 9α-bromo-11-keto progesterone when given to estrogen-primed, castrated women and found it more active than 17α-ethinyl testosterone and about as active as 19-nor-17α-ethinyl testosterone when given by mouth.

In addition to the differences in the intensity of progestational activity, the duration of action of a single dose and the most favorable mode of administration, the numerous progestational steroids differ from one another and from progesterone in other ways. They were selected primarily as a result of their ability to induce a secretory endometrium. This, however, is but one parameter of the spectrum of hormonal influences of progesterone. Other important actions are the ability to suppress pituitary gonadotropin secretion, preserve pregnancy (tested in ovariectomized animals), promote growth of breast parenchyma and lactation, the metabolic influence (enhanced catabolism and aldosterone inhibition), and others. When compared on the basis of some of these indices the synthetic progestins fall short of mimicking the action of progesterone here and there. The interested reader is referred to original papers for details (30, 76 to 79, 82).

There have also been a number of examples of overlap in hormonal action Some of these have already been mentioned in previous sections 17α-methyl-19-nortestosterone was so androgenic as to be useless as a progestin (79), and 17α-ethyl-19-nortestosterone and 17α-ethinyl-19-nortestosterone were weak androgens (24, 29, 30). The latter compound as well as norethynodrel possessed some estrogenic activity (30, 70, 80, 81).

In surveying the reports describing new progestational steroids one soon becomes aware of the fact that compounds have been proposed, synthesized, and tested in at least a preliminary manner more rapidly than the new facts could be assimilated and placed in proper perspective. In part, this has arisen from the fact that a potential drug has been "pushed," often quite appropriately, for a specific clinical use. Thus, one progestational steroid has been studied predominantly as an anabolic agent with negligible androgenicity, another as a gonadotropin inhibitor, a third as a pregnancy supporting agent, etc. Investigators who have studied one parameter have not been able to pay much attention to others Furthermore, the new progesta-

ceived some trials, 17α-hydroxy progesterone caproate seems to have been most extensively tested. The results reported from all centers are in agreement that treatment with progestational compounds substantially decreased the frequency of abortion. This has been another difficult study to construct and execute. Some groups have used the previous experiences of the patient (in habitual aborters) as the controls. Others have divided the patients into two groups treating one with the progestin and the other in some acceptable nonspecific fashion. Either approach has its methodological and statistical defects as has been vigorously pointed out (96). Nonetheless, the unanimity of the results reported to date is impressive.

In view of the reports of pseudohermaphroditism in infants following treatment of the mother with 17α-ethinyl testosterone, this reviewer would feel obliged to avoid the use of the more potent anabolic and weakly androgenic 19-nor-17β-OH progestational compounds for this purpose (see next section).

GONADAL DYSGENESIS AND HERMAPHRODITISM

Barr's very important discovery of sexual dimorphism in cell nuclei has made it possible to distinguish the genetic sex of human tissues, leading toward a greater understanding of several puzzling syndromes Barr and his colleagues (104, 105) observed that most nuclei of females usually contain a characteristic heterochromic mass and that this was seldom seen in the nuclei of male tissues. It has been proposed that the mass of dark staining chromatin represents either the XX chromosones or, according to another concept, the site of autosomal suppressed male determinants (106). Using this technique Polani, Hunter & Lennox (107) followed by other workers (108) showed that about 80 per cent of women with the syndrome characterized by sexual infantilism, short stature, amenorrhea, high gonadotropin titers in the urine and scattered congenital anomalies (ovarian agenesis, gonadal dysgenesis, Turner's syndrome) exhibited the male-type of chromatin pattern in their cells. Subsequently, three groups of workers (109, 110, 111) reported that in Klinefelter's syndrome (men with seminiferous tubule sclerosis, high urinary gonadotropin titers, gynecomastia, and variable hypoandrogenism), many of the patients had female chromatin patterns. These unexpected discoveries have excited a great deal of interest.

Segal & Nelson (106), Grumbach, Blanc & Engle (112), Plate (116) and Witschi, Nelson & Segal (113) have each proposed sensible concepts which bring together the clinical findings and the results of a number of studies in experimental embryology to form more or less integrated explanations for the development of the above syndromes, pseudohermaphroditism, and true hermaphroditism. The interested reader is referred to these articles which do not differ greatly, but tend to supplement each other at several points.

TURNER'S SYNDROME

In vertebrates, regardless of the genetic sex of the embryo, the early or primordial gonad has a potential testicular and a potential ovarian compo-

vented anovulatory bleeding—often even after discontinuing this treatment (83, 85, 86, 87).

In combination with estrogens, progesterone or, more easily administered, long-acting and oral progestins, have enabled the therapist to simulate the normal menstrual cycle in amenorrheic women (bleeding, temperature elevation, breast changes). This has been useful psychologically, at least, in some patients. The idea that repeated courses might be followed by the resumption of normal cycles has, on the whole, been disappointing (85, 86, 87, 137). A few normal spontaneous periods have followed such treatment, and on occasions there have been pregnancies. However, the percentage of successes has been small and, in one comparison, not convincingly greater than in a small series of controls who had received no treatment (85, 88). The statistical approach to the solution of this difficult problem could be misleading. Amenorrheics as a group, probably include several types of ovarian or pituitary disturbances or both. When the pathologic physiology of each of these types has been elucidated, it may be that certain cases which could be lost in a statistical shuffle, will be peculiarly susceptible to cyclic treatment with progesterone and estrogen.

Gonadotropin Inhibition

For the future, perhaps the most important application of some of these new progestational agents will be as gonadotropin inhibitors (101, 103, 137). Rock, Pincus & García (89, 90) have studied extensively the potent oral progestins, norethynodrel, 17α-ethinyl-19-nortestosterone, and 17α-ethyl-19-nortestosterone When these were administered to normal women in doses of 10 to 20 mg per day from day 5 to day 25 of the cycle ovulation was completely suppressed. The first two compounds had some inherent estrogenicity, the latter none As a consequence, the incidence of "break-through" bleeding was considerably greater when 17α-ethyl-19-nortestosterone was used The addition of a small amount of estrogen diminished the frequency of break-through bleeding even with the two more favorable drugs. There was also a significant incidence of other side effects if the courses were repeated. Nausea and other gastrointestinal symptoms and psychologic reactions were the more frequent In a series of 1279 cycles in which women received this suppressive treatment no pregnancies occurred despite the fact that the women were frequently exposed Normal ovulatory cycles resumed promptly after this treatment was stopped, indicating that the sensitive gonadal-pituitary system had not been permanently impaired.

The inhibition of ovulation may also be of value in the treatment of severe cases of dysmenorrhea and perhaps even endometriosis.

Preservation of Pregnancies

A number of investigators have been attempting to improve the salvage [illegible] with threatened abortions, by the [illegible] ogesterone or one of the newer [illegible] the newer compounds have re-

All of the "true" Klinefelter's syndrome cases had female chromatin patterns in their cells whereas the "false" syndrome was found only in males. All observers (116) have not agreed with Nelson in this breakdown of the syndrome, but there is no disagreement on the point that a substantial number of patients with Klinefelter's syndrome do have female chromatin sex patterns.

The development of this syndrome appears to be the result of a damaged or defective primordial gonad in which the male or medullary portion persists and apparently dominates the cortical or ovarian component. In the absence of a significant functioning ovarian anlage, the medulla goes on to develop into at least the elements a testis even if the predetermined genetic sex of the organism was female. In the genetic females this would appear to be an example of almost complete sex reversal. There is some suggestion that the defect in Klinefelter's syndrome may be genetically determined for, on occasion, several cases have been observed in one family (112).

Male Pseudohermaphroditism

This is a rare condition in which individuals who have the external physical attributes of women have male gonads which are usually intra-abdominal and resemble cryptorchid testes. Pubic and axillary hair may be absent or normally distributed for a woman. As a rule, the Wolffian duct derivatives are intact with vestigial Müllerian derivatives, but there is a normal vagina. The disorder has a pronounced familial predilection, careful studies suggesting that if individuals with this syndrome are considered as males there is a normal sex distribution. All of the patients with this disorder whose cells have been examined have been shown by this criterion to be genetic males.

It has been suggested (111) that at about mid-term after the more proximal elements of the Wolffian duct system have developed, an antitestis factor comes into play. Since the caudal elements of the Wolffian system are usually not completed at this time the external genitalia, developing in a neutral milieu, become those of a normal female. These testes at puberty and thereafter apparently secrete feminizing quantities of estrogen.

Female Pseudohermaphroditism

This condition is usually the result of congenital adrenal hyperplasia. The pathologic adrenals begin secreting unusually large quantities of androgen sometime between the tenth and sixteenth week of gestation. At this point the Müllerian duct derivatives have almost completed their development *into female* accessory sex apparatus. The androgen accordingly can affect only the latter phases of secondary sex differentiation, and the development of the phallus, the labioscrotal folds and the ureogenital sinus are diverted in a masculine direction. The genetic sex of these individuals is always female.

The female pseudohermaphroditic condition has also occurred as a result

nent. The medulla of the gonad can only develop into a testis and in genetic males the cortical portion ultimately disappears. The cortex of the primordial gonad in genetic females develops into the elements of the ovary, and the medullary components fade away to negligible residuals.

The studies of Jost (114) and others have shown that removal of the primordial gonads prior to differentiation into testes or ovaries is followed by the development of the Müllerian duct derivatives into the female secondary sex structures. The development of the female genital tract does not seem to require the presence of ovaries or of ovarian secretions and have accordingly been termed neutral. Male organizing substances (perhaps male hormones) passing from the embryonic testes cause the Müllerian derivatives to atrophy and induce the growth and development of the Wolffian ducts into the male accessory structures as well as the development of the male external genitalia.

As a rule in Turner's syndrome, only a small ridge is present at the expected site of ovaries and microscopic examination reveals minimal gonadal remnants or more often none at all. A very small uterus and fallopian tubes are present. It has been suggested that this picture results from atrophy or failure of the embryonic gonad prior to differentiation. Thus, whatever the genetic sex of the embryo the absence of any gonadal organizing substance permitted neutral development of the accessory sex apparatus Witchi (113) has suggested that the failure of gonadal development may be the result of delayed fertilization or some injury in the fertilized ovum prior to implantation. The associated defects which are so frequently seen, and the lack of any suggestion of familial occurrence of the disorder are consistent with this view.

The predominance of what are apparently genetic males in this syndrome has not so far been satisfactorily explained. It has been suggested, however, that the deficiency in females may be made up by individuals with only a partial failure of the female elements of the primordial gonad. Such partial defects might well result in women of short stature with some secondary sex characteristics and oligomenorrhea or perhaps women with primary amenorrhea and no other stigmata, etc.

It is almost unnecessary to state that no one thus far has suggested that girls with gonadal aplasia and male chromatin patterns should be raised as boys.

Klinefelter's Syndrome

Nelson (115) has re-examined the testicular biopsy specimens in a series of 67 patients with Klinefelter's syndrome. All had seminiferous tubule sclerosis, but he was able to divide them into two groups, "true" Klinefelter's syndrome in which the tubules were small in diameter with all but a few completely hyalinized, and the "false" syndrome in which much the same picture was seen except that the tubules were much larger suggesting that the testes had been sclerosed postpubertally perhaps by some infection.

gestions of adrenocortical dysfunction. In a group of eight women with amenorrhea or anovulatory oligomenorrhea, hirsutism, and borderline or slightly elevated urinary 17-ketosteroid excretion, treatment with cortisone acetate in doses of 25 or 50 mg. per day led to the resumption of apparently ovulatory menstrual periods and induced a sharp suppression in 17-ketosteroid excretion. Several pregnancies followed. In patients with the Stein-Leventhal syndrome, which may be defined as the association of polycystic ovaries, amenorrhea or oligomenorrhea, infertility, and often hirsutism and obesity (124), the results of cortisone therapy were not so uniformly helpful. In this rather ill-defined group of patients urinary 17-ketosteroid excretion was usually within the normal range initially.

The improvement in ovarian function induced by cortisone in hirsute women with menstrual disturbances has now been observed by other groups (125, 126, 127), and has led to the general assumption that an excessive secretion of adrenal androgen was responsible for both the hirsutism and the ovarian dysfunction. Women with hirsutism and normal menstrual cycles may also exhibit a sharp drop in urinary 17-ketosteroid excretion when treated with modest doses of cortisone. Kappas *et al.* (128) reported one case of such hirsutism with a 17-ketosteroid excretion of 25 mg. per 24 hr. Of considerable importance was the fact that the excretion of androsterone and etiocholanolone was three times greater than the normal average for women of that age The excretion of these two 17-ketosteroids dropped to a normal level with cortisone treatment and surprisingly remained normal during repeated assays for 24 months after treatment had been stopped. The Memorial Hospital group (129) then carried out similar studies on thirteen successive cases of hirsutism (nine with regular menses and four with the Stein-Leventhal syndrome), and in all of them the excretion of androsterone and etiocholanolone was decidely elevated (average 2½ times normal). Excretion of 11-hydroxylated 17-ketosteroids which are derived from hydrocotisone also tended to be slightly elevated in this group Perloff and his associates (130) have confirmed these findings Nobody has as yet reported a conspicuous loss of the excessive hair growth in any of these patients It was assumed by Gallagher *et al.* (129) that androsterone and etiocholanolone which, in men are the principal urinary 17-ketosteroids derived from testosterone, are derivatives of the adrenal androgen, and that the excretion pattern in these hirsute women is indicative of an enhanced secretion of this hormone

The easiest conclusion to be reached from this series of studies is that a pathologic excess of the secretion of an androgenic hormone by the adrenal cortex may produce only an excess of body hair in some women In others ovarian function may also be suppressed, and in still others, polycystic ovaries (Stein-Leventhal syndrome) may develop On rare occasions an excessive output of a noncorticoid adrenal secretion (androgen or perhaps estrogen or progestin) may apparently suppress ovarian function without producing any physical stigmata of the endocrine disturbance (125).

The surprising fact that in some of these women with hirsutism and

of exposure of the embryo to excessive androgen of maternal or placental origin. Treatment of the mother with testosterone, methyltestosterone, or other androgens at the critical time of embryonic development has resulted in several pseudohermaphroditic babies (117, 118). Wilkins & Jones (119) and others (120, 121) have described a number of such cases in which the crucial factor seems to have been the fact that the mothers had been given 17α-ethinyl testosterone or, in a very few instances, progesterone, because an abortion was threatened or they were habitual aborters. In none of these infants was urinary 17-ketosteroid excretion elevated and there were no other tests which suggested adrenal hyperplasia. In such children the only treatment required would be plastic surgery. Normal spontaneous sexual maturation would be anticipated without the suppressive treatment with cortisone required in adrenal hyperplasia.

In three of the cases reported by Wilkins & Jones (119) the mothers had received no hormonal therapy but it is important to note that a history suggestive of excessive androgen secretion (seborrhea, acne) during the critical period of the pregnancy was elicited in each of them suggesting a transient increase in the level of circulating androgen. Whether this represented altered steroid metabolism or pathologic secretion remains to be determined. It is also quite possible that a metabolic derivative rather than 17α-ethinyl testosterone itself was responsible for the masculinization in the patients noted above. In either case this distressing complication must be kept in mind when considering the treatment of a woman in the early months of pregnancy with some of the new 17β-OH-19-nor progestins.

True Hermaphrodites

The classical true hermaphrodite is an individual with at least the elements of both testes and ovaries Several types have been described. In some, one finds ovotestes, in other ovotestes on one side and either an ovary or testis in the other and finally an ovary on one side and a testis on the other. With any of these combinations there has usually been an ambisexual development of the accessory sex ducts and external genitalia. The genetic sex of these individuals may be either male or female but in the relatively few cases examined, females have predominated. One explanation offered for the development of these defects is the existence of imbalance between the [illegible] elements of the gonad so that the cortex [illegible] dominate in the [illegible] yonic gonad persist into adulthood.

OVARIAN DYSFUNCTION AND HIRSUTISM

Following the dramatic demonstration by Wilkins and his associates (122) that in patients with congenital adrenal hyperplasia cortisone would suppress the excessive androgen secretion and permit normal ovarian function, Seegar-Jones, Howard & Langford (123) reported success in the similar management of some women with menstrual disturbances and some sug-

gators feel that at least some of these functional abnormalities are genetically determined. Despite the fact that none of the endocrine analyses have pointed to a hormonal etiology in any significant number of these cases, this possibility cannot be neglected. The integrity of the seminiferous epithelium is so dependent upon the maintenance of a rather delicate hormonal balance [illegible]

conditions may closely resemble the hypospermatogenesis seen in some infertile men.

From all indications the prognosis in the treatment of hypothetical cases in which endogenous endocrine products had suppressed spermatogenesis would be excellent. In one instance, hypospermatogenesis induced by an estrogen-secreting adrenal tumor which had been present for 16 years was dramatically improved after removal of the neoplasm (142). Perloff (143) recently described a case in which prednisone therapy appeared to improve the quality of ejaculates in a man with a biopsy evidence of hypospermatogenesis Urinary 17-ketosteroid excretion was moderately elevated and was easily depressed to normal levels by the corticoid. It was presumed that the adrenals in this case were secreting unusual quantities of an androgen It is possible that similar cases may not be characterized by an excessive excretion of the total urinary 17-ketosteroid mixture In the search for such cases, urinary pregnanetriol, which may be elevated in the adrenogenital syndrome, was estimated in 20 men with hypospermatogenesis and spermatogenic arrest, and in none of this small series was pregnanetriol excretion elevated (144).

The enzymatic approach to the study of spermatogenic abnormalities is promising Weir & Leuchtenberger (145) noted that the deoxyribose nucleic acid content of sperm, as measured by a microspectrophotometric procedure, was abnormally low in infertile men whether or not the donor was oligospermic Nelson (146) demonstrated for the first time that adenosine triphosphatase was localized in the nine longitudinal fibers of the outer axial fiber bundle of the flagellum This has been related to the fact that adenosine triphosphate is vital in supplying energy for fibrillar contraction.

The treatment of patients with oligospermia remains uncertain. In what is admittedly a difficult area of investigation, sloppy experimental design and poor statistical methods have created confusion (149) The observations of Heller (147) and Heckel (148) that in oligospermic patients the suppression of spermatogenesis with large amounts of androgen may be followed by a rebound to normal levels of spermatogenic activity has only been partially confirmed, if at all Although there is no rational guide to this form of treatment, it is certainly possible that a critically selected type of defect might be responsive to this sort of treatment If, as it would seem, this is a relatively rare disorder, an occasional success might be lost in a large series of patients of various types unsuccessfully treated in the same way. At the

menstrual disturbances the ketosteroid excretion may remain normal and the menstrual periods ovulatory for months after a relatively short course of cortisone contrasts sharply with the rapid reversibility of the adrenal suppression after treatment has been stopped in congenital adrenal hyperplasia It suggests that these women may have an acquired abnormality in secretory function which in some manner can be set aright by treatment with a relatively short course of an adrenal corticoid.

Most of the recent students of these disorders have tended to neglect the possibility that the ovaries themselves could be the source of the excessive androgen in some of these patients. The peculiar fact that a wedge resection of the polycystic ovaries in the Stein-Leventhal syndrome is often followed by ovulatory periods and pregnancy would seem to point toward a primary ovarian rather than an adrenal disorder in this syndrome at least. Functioning ovarian tumors may produce varying degrees of virilization as well as ovarian failure, and experimental studies in laboratory animals have shown that normal ovaries have the capacity to secrete androgen (131). In a recent study carried on in a patient with a virilizing arrhenoblastoma it was disclosed that although the total 17-ketosteroid excretion was not elevated the excretion of androsterone and etiocholanolone was several times the normal level (132). Thus, the ovaries have the capacity to produce virilizing quantities of an androgen whose derivatives in the urinary 17-ketosteroid pool are the same as those from the testis and the adrenal cortex.

MALE INFERTILITY

Our understanding of male gonadal defects leading to infertility is, on the whole, poor. To be sure there are some syndromes which have been reasonably well worked out, but they comprise a small minority of the total number of cases. Klinefelter's syndrome has been discussed. In hypogonadism secondary to an hypophyseal defect the gonadotropin deficiency may be the sole pituitary abnormality, or this may be just one manifestation of a broader hypopituitary state. On occasions in the former types, the gonadotropin activity found in pregnant women's urine (gonadotropin which is predominantly interstitial cell-stimulating but has some follicle-stimulating activity) seems to match the deficiency so perfectly that not only were the Leydig cells stimulated to secrete adequate amounts of androgen, but normal spermatogenic activity was induced (133) Pregnancies in partners of such patients have been observed. The occasional successes warrant trials with this material in all such patients who are interested When the eunuchoidism arises primarily from testicular failure, there is no treatment for the spermatogenic failure.

The vast majority of men with spermatogenic defects have no endocrine stigmata. In a substantial number of these the seminiferous epithelium has been damaged by some inflammatory disease. The remainder have been grouped into several categories in accordance with the type of disturbance visualized in the testicular biopsy specimens (134, 135, 136). Some investi-

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moment, however, MacLeod's skepticism as to the value of testosterone suppressive treatment seems justified.

There has also been a flurry of interest in the use of triiodothyronine in the treatment of oligospermia (150, 151, 152). Some success has been reported, but this requires a good deal of corroboration. Since desiccated thyroid has never been shown to be specifically effective, except in proven hypothyroidism, it seems proper to doubt the rather frequent effectiveness of triiodothyronine which has been reported.

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ENDOCRINOLOGY (SURGERY OF THE ENDOCRINES)

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The literature covered herein embraces the period from July 1, 1957, through June 30, 1958. Some articles were omitted because they did not bear directly upon the rather sharply circumscribed assignment. The endocrine response to surgery has been included. The review is confined to publications in English. Rather than merely to acknowledge briefly the contents of a series of disconnected articles, we have charted a rather deliberate course through the field of "surgical endocrinology," taking due note of the publications encountered along the way. The objective has been to provide both a balanced discussion and an effective survey of the pertinent recent literature.

In view of both space and subject limitations, some rather arbitrary restrictions have had to be imposed. The following topics will be considered: (*a*) the endocrine response to major surgery; (*b*) hypophysectomy for advanced cancer; (*c*) the thyroid; (*d*) the parathyroids, (*e*) the thymus; (*f*) the pancreas (limited to diseases of the islets of Langerhans), (*g*) the adrenal cortex; (*h*) the adrenal medulla; and (*i*) the ovary and testis.

THE ENDOCRINE RESPONSE TO MAJOR SURGERY

The hormonal alterations and interrelationships which follow major operations continue to interest surgical endocrinologists intensely. Nevertheless, there is a growing awareness that the endocrine system is responsible for only a part of the metabolic phenomena which commonly are observed after trauma—and that this role may be more "permissive" than "stimulatory" (Fig. 1). Moore (36, 37) has reviewed the generally accepted mediators of surgical injury, with specific examination of the endocrine changes after anesthesia, surgery, and unanesthetized trauma in man. The general pattern of this response has been established for a number of years, but further definition and amplification continue. It is noted that the major hormonal effects are reflected in an increased secretion of adrenal corticosteroids, the adrenal medullary catechol amines epinephrine and norepinephrine, and the antidiuretic hormone of the posterior pituitary.

The hydrocortisonelike corticosteroids result in, or at least permit, the diffuse metabolic stress phenomena that are familiar to all. The interplay between aldosterone and the antidiuretic hormone may be, in considerable measure, responsible for the antidiuresis (28) frequently observed following injury. The catechol amines result in a mobilization of glycogen from the liver and in generalized vasoconstriction.

Among the nonendocrine factors which may, themselves, influence the

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tive in fish but not in rats, while bovine extracts were effective in both fish and rats. Thus, the apparent ineffectiveness of bovine or porcine growth hormone in altering the post-traumatic metabolic response in human beings may result from the fact that these compounds are relatively ineffective in man, where a compound more nearly similar to the naturally occurring human growth hormone may be required.

Feedback mechanisms.—The endocrine response to surgery is essentially a normal and self-limiting response, though the self-limitation may represent the countereffect of physiologic feedback mechanisms. An example of this type of relationship is seen in the diminished pituitary secretion of ACTH which follows hydrocortisone therapy. The ACTH-induced adrenocortical hypersecretion following surgery may thus be self-limiting in a similar manner, as may other segments of the metabolic response to trauma.

The Adrenocortical Response to Surgery

Additional data regarding postoperative adrenocortical function have further documented existing concepts (9, 21, 34, 42). It is now well accepted that surgery usually results in a rise in the plasma "hydrocortisone" levels and in the urinary excretion of corticoids.

Plasma 17-21 hydroxycorticosteroid levels in infants.—The effect of surgery upon the plasma levels of 17-21 hydroxycorticosteroid levels in infants (largely hydrocortisone) has been evaluated (53) by means of a microtechnique. In a study of 11 patients, it was found that adrenocortical activity did increase following operation. The general pattern of response was similar to that in adults, but the postoperative rise in plasma corticoid levels was less marked in infants For example, the level of free 17-21 hydroxycorticosteroids in the control specimen averaged 2 73 gamma/100 ml of plasma, while the conjugated forms averaged 1.27 gamma/100 ml. of plasma; four hours following surgery these levels had risen to 5 36 and 2 57 gamma/100 ml, respectively. These control values were approximately 30 to 50 per cent, and the postoperative rise approximately 25 to 30 per cent, of those usually found in adults

Studies of Adrenal Vein Blood

A technique has been described for obtaining timed samples of adrenal vein blood at laparotomy (17) Essentially, the left central adrenal vein is exposed and cannulated. Most of the venous outflow from the left adrenal in man courses through this vessel and thence into the left renal vein It is thus possible to determine hormone levels in adrenal blood as compared with peripheral blood, and to achieve approximations for the total output of a particular hormone per 24 hr.

Hydrocortisone—In 10 patients, the average level of free 17-21 hydroxycorticosteroid in adrenal vein blood was 224 gamma per 100 ml., as compared to 24 gamma per 100 ml. in peripheral plasma The values for conjugated steroid were 125 and 16.7 gamma per 100 ml, respectively. It has been

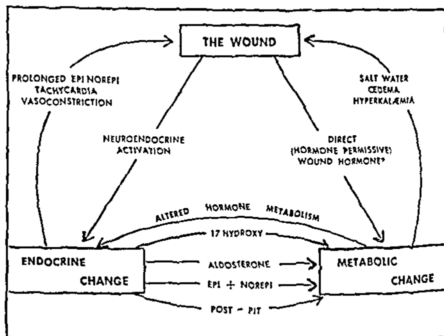


FIG. 1. The wound, the endocrine change, and the metabolic change all influence each other (37) Epi = epinephrine, norepi = norepinephrine; post-pit = posterior pituitary antidiuretic hormone; 17-hydroxy = 17-hydroxycorticosteroids. [From Moore, F. D. (37), and Moore, F. D., "Metabolism in trauma," *Harvey Lectures*, 74–99 (1956–57)]

endocrine system as well as other important segments of postoperative metabolism are brain injury, pulmonary ventilatory insufficiency, tissue necrosis, shock, infection, starvation, sex, nutritional state of patient prior to surgery, type of operation performed, and surgical complications other than those already given (29) "Hospital starvation," both during the course of preoperative diagnostic studies and following surgery, often assumes a major role in determining the quality of the convalescence.

Pituitary growth hormone.—Growth hormone has thus far been disappointing when used to diminish post-traumatic catabolism and to promote anabolism. However, it has recently been pointed out that there are important chemical and physiologic differences between growth hormone preparations derived from human or monkey pituitary glands as compared with those derived from bovine or porcine sources (24) While the physiological effects of growth hormone of bovine or porcine origin can readily be demonstrated in small laboratory animals, the results in man and in monkeys have been essentially equivocal Furthermore, there are chemical and physical differences between growth hormone from ox, sheep, pig, horse, and fish pituitaries; and growth hormone isolated from fish pituitaries was effec-

in plasma sodium and extracellular volumes did cause a further increase in aldosterone secretion.

It was concluded that aldosterone is probably not entirely responsible for the protracted period of sodium concentration which follows surgery, and that it may act only as an initiating or "trigger" mechanism. Although the means by which aldosterone excretion is stimulated by surgery could not be determined, since neither the extracellular volume nor the plasma electrolyte level appeared to be the critical factors, it was suggested that direct stimulation of centers in the central nervous system might constitute important underlying mechanisms.

The Adrenal Cortex and Blood Coagulation

Williams & Warren (51) have studied *in vitro* the effect of 17-hydroxycorticosteroids on prothrombin consumption and on the clotting time with and without heparin It was observed that the addition of "physiologic" amounts of 17-hydroxycorticosteroid elevated the serum concentration of this substance to levels corresponding to those observed in the early postoperative period; there was consistently an acceleration of the clotting time and an increased prothrombin consumption. It was concluded that adrenocortical hormones may play an important role in conditioning the clotting segment of the total biologic response to stress.

The Adrenal Medullary Hormones

Although it was pointed out previously that the adrenal medullary response to trauma constitutes one of the major endocrinologic changes commonly observed, particular mention should be made of the extensive work of Hume (23), who has continued his previous technique of cannulating the adrenal vein in dogs and studying the effects of various stimuli, including shock and surgical trauma, upon the rate of secretion of the catechol amines, epinephrine and norepinephrine. The corticosteroid secretion was also measured, in order to correlate the rate of the secretion of these steroids with that of the catechol amines There was found to be a marked difference in the rate of secretion of epinephrine in the dogs that were anesthetized with ether as compared with those anesthetized with pentobarbital sodium (Nembutal), the former being much higher There was relatively little difference in the rate of secretion of the corticoids. Ether anesthesia alone produced an increased adrenal secretion of epinephrine, norepinephrine, and 17-hydroxycorticosteroids over that seen in the resting conscious dog. Operative trauma under ether anesthesia produced an additional increase in epinephrine and norepinephrine secretion, even in the presence of profound shock. Corticosteroid secretion was increased also, except when the shock was so severe as to lead to a marked decrease in adrenal blood flow Barbital anesthesia, alone, depressed the secretion of epinephrine and norepinephrine. Operative trauma under pentobarbital was accompanied by a

estimated that during stress the rate of hydrocortisone secretion may be on the order of 111 mg./24 hr., and under normal conditions perhaps 34 mg./24 hr. The calculations were based solely on plasma values; if a 25 per cent increment be added for red cell content, a value of 47 mg. is obtained for the "normal" 24-hr. secretion. These values for hydrocortisone secretion agree remarkably well with those obtained previously by the use of indirect methods. In addition to the correlation of adrenal vein hydrocortisone levels with those in peripheral plasma, the sites, mechanisms, and significance of hydrocortisone conjugation are discussed (17).

Estrogens and 17-ketosteroids.—The estrogen and 17-ketosteroid concentrations in adrenal vein blood taken during operation were compared with those in peripheral blood before, during, and following operation (18). In a few instances, it was possible to obtain ovarian venous plasma estrogen determinations for comparison with levels in adrenal venous blood and in peripheral blood. The adrenal plasma estrogen and 17-ketosteroid levels sharply exceeded those of peripheral blood. Both the ovary and the adrenal gland are capable, as again shown in these studies, of secreting significant amounts of both "estrogens" and "17-ketosteroids." The surgical trauma did not affect the plasma 17-ketosteroid level.

Aldosterone

The pattern and significance of aldosterone secretion by the postoperative surgical patient were examined by Casey & Zimmerman (3). These workers emphasized that the rather consistent group of metabolic reactions which characterize the response of patients undergoing major surgical procedures need not all represent entirely parallel or mutually interdependent processes. For example, it is pointed out that the extreme degree of renal conservation of sodium which usually begins immediately after surgery is more prolonged than the protein catabolic phase. Furthermore, this chronologic relationship suggests that if adrenal participation is responsible for the postoperative changes in both the organic and inorganic aspects of metabolism, then separate hormones or groups of hormones must be involved, presumably stimulated by different pathways or mediators. In line with this, it is well recognized that the adrenal regulation of sodium and potassium balance is not, to any great extent, subject to pituitary adrenocorticotropic activity. That is, the zona glomerulosa appears to be largely independent of pituitary stimulation. In their studies of six patients for the purpose of evaluating the role of aldosterone in the regulation of postoperative electrolyte responses, these workers determined the sodium, potassium, and chloride balances, together with the blood levels of these ions. The data were correlated with the urinary excretion of aldosterone and 17-hydroxycorticosteroids The maximum aldosterone levels were found early in the postoperative period, and the elevated excretion of this steroid did not persist throughout the period of positive sodium balance. There was little correlation between the aldosterone output and the plasma concentration of sodium or other ions. A secondary fall

later prednisone were administered orally. Diabetes insipidus developed on the day of operation but was readily controlled. Subsequently, there was a steady fall in the rate of 17-ketosteroids to 47 mg./24 hr. (preoperative level, 203 mg.). The excretion of other steroids also declined. There occurred marked improvement in the patient's acne, and the rate of growth of facial hair was definitely reduced. Furthermore, there appeared to be some improvement in the pulmonary metastases, as two small lesions became invisible on chest x-ray, only to reappear three weeks later. Unfortunately, despite the early reduction in the rate of excretion of steroids, the level began to rise again within one week following hypophysectomy. Furthermore, it was clear that hypopituitarism had been achieved by hypophysectomy. The diabetes insipidus persisted and hypothyroidism developed. Although the radioiodine uptake was not reliable because of a previous intravenous pyelogram with an iodide-containing compound, the serum cholesterol level rose from 169 to 322 mg./100 ml., two weeks following the operation. Moreover, there were symptoms which suggested hypothyroidism, and this responded rather satisfactorily to the administration of triiodothyronine. Despite these evidences of hypopituitarism, however, at autopsy weeks later there was found to be a small remnant of anterior pituitary cells beneath the dura of the sella turcica.

In concluding this discussion of pituitary pathology, it should be mentioned that opinion is again swinging toward the view that the basophil adenoma may have more significance in the pathogenesis of Cushing's syndrome than has been fully appreciated in recent years. That is, certain changes which often reflect the presence of a pituitary tumor may not be abolished by even total adrenalectomy, though the conspicuous features of adrenocortical stimulation can be thus controlled. The patient may return months later with evidence of continuing pituitary pathology, such as hyperpigmentation, visual field defects, and headaches. This is in partial conflict with the thesis that Cushing's syndrome is due to ACTH-induced adrenocortical hyperplasia (where there is no tumor), and that the condition is satisfactorily managed by adrenalectomy—as hyperthyroidism is controlled by subtotal thyroidectomy even though the thyroid-stimulating hormone (TSH) stimulus for the hyperthyrodism may arise in the pituitary.

THE THYROID

The use of radioactive iodine in the therapy of hyperthyroidism, as an alternative to surgical excision or as a palliative agent in recurrent hyperthyroidism following surgery, is now so well accepted that little comment has appeared in the recent surgical literature. In medical centers where radioiodine is readily available, an increasing percentage of patients with both diffuse and nodular toxic goiter are so treated. On the other hand, where radioactive iodine therapy is not available, subtotal thyroidectomy is still used following suitable preparation with iodine or one of the antithyroid drugs.

marked increase in corticosteroid output, but there was no significant increase in epinephrine and only a slight increase in norepinephrine secretion. An increase in adrenocortical secretion began within 3 min. after injury and an increased medullary secretion, when it occurred, appeared even within 2 min. after injury. As others have found in human beings, a second operation during convalescence produced an adrenal response which was equal to or greater than that seen at the first operation.

HYPOPHYSECTOMY FOR ADVANCED CANCER

In the past few years, much interest has surrounded the use of hypophysectomy as a further extension of the endocrinologic management of far advanced cancer. It has been appreciated that in the living subject the best available index of the completeness of the hypophysectomy, even though a crude one, is the subsequent activity of endocrine organs dependent upon a pituitary tropic hormone The most striking changes observed have been reduced adrenocortical activity and symptomatology suggestive of the development of a myxedematous state caused by diminished thyroid activity. Moreover, diabetes insipidus has appeared in the majority of patients. The resulting polyuria and polydipsia have varied in severity from one individual to another, but the state has usually been rather easily controlled by the use of vasopressin, often administered by nasal insufflation of the powder. Unfortunately, the palliative effect upon the tumor has usually been rather limited.

Hypophysectomy for functioning metastatic adrenal carcinoma.—Recently, Sobel *et al.* (46) have studied the effect of hypophysectomy and other measures in the management of a functioning metastatic adrenal carcinoma. In view of the fact that functioning adrenal carcinomas usually present a formidable problem in management unless complete surgical removal can be accomplished, it was felt that more heroic measures than the usual recourse to radiation or to usual chemotherapy should be employed. The patient was a girl who was under metabolic studies from the age 7 years, 7 months until her death at 7 years, 10 months. Surgical excision of an adrenal carcinoma, which was followed by radiation of the tumor bed, was undertaken at the age of 7 years and 3 months, 3 months after the first manifestation of virilism. The immediate response had been gratifying, but symptoms recurred, associated with a palpable mass in the left lower quadrant of the abdomen. Lung metastases appeared at the age of 7 years and 5 months. Shortly after the age of 7 years and 7 months, the signs of Cushing's syndrome with moderate hypertension became evident and rapidly increased. The virilism became marked and the hypertension rose to 200/120 mm. Hg, along with striae, voracious appetite, and glucosuria. Inasmuch as there was some evidence that the tumor was dependent upon pituitary stimulus with corticotropin, hypophysectomy was performed using a transfrontal approach. The patient received 300 mg. of hydrocortisone intravenously the day of operation; thereafter decreasing doses of cortisone and

THYROIDITIS

Chronic thyroiditis continues to present difficult problems in surgical practice. In general, the problems resolve themselves into the differentiation of thyroiditis from cancer and the management of the pressure effects of the more serious forms of the disease Witebsky *et al.* (52) have sought an explanation for chronic thyroiditis in man through observations on rabbits, dogs, guinea pigs, and human subjects Proceeding upon the hypothesis that the disease might arise from autoimmunization, they injected rabbits with saline extracts of rabbit thyroid glands. The tests for circulating autoantibodies utilized the phenomena of precipitation, complement fixation, and tanned-cell hemagglutination. Structural damage was found in the thyroid gland that was roughly proportional to the autoantibody titer in the serum. Applying the three tests to the serums from individuals with chronic thyroiditis, 12 were found whose serums contained circulating antibodies specifically directed against extracts of human thyroid glands However, six other patients with chronic thyroiditis, proved histologically, were not found to have autoantibodies in their serum at the time of the study. It was concluded that some types of chronic thyroiditis are related to an autoimmunization process within the patient against his own thyroid tissue.

SURGICAL MANAGEMENT OF THYROID CANCER

The controversy—The extent of surgical resection for the management of thyroid cancer and, in particular, papillary adenocarcinoma of this gland constitutes one of the most controversial and heatedly discussed problems in surgical practice at the present time. At one extreme are those who feel that this actually represents an almost benign condition, since the patients usually live for 10 or 15 or more years, even though eventually a sizable percentage of the patients do die of the cancer. At the other extreme are those who believe that thyroid cancer should be treated as any other cancer, with total thyroidectomy and an *en bloc* radical neck dissection Thus far, the present writer aligns himself with this second group. Finally, there are many intermediate shades of opinion To further complicate the picture, it has been found in recent years that thyroid tumors will regress under certain forms of hormonal therapy which will be described below under the "medical" management of these malignancies

Survey of sixty-four thyroid cancers—Sixty-four cases of carcinoma of the thyroid managed at the Walter Reed Army Hospital have been reported by Jay *et al.* (27) It is again brought out that carcinoma of the thyroid is more common in females and in the young adult. Papillary adenocarcinoma was the most common malignancy in all three age groups, with follicular carcinoma second. Older patients tended to have more malignant tumors Of the 64 cases, papillary adenocarcinoma was found in 41, follicular in 18, and other types in the other 5 Although the follow-up of this group was too short to quote mortality rates and longevity, it was noted that three of the patients

The Diagnosis of Hyperthyroidism

Erroneous diagnoses.—Jackson (26) has analyzed a series of 228 cases in which surgery had been advised elsewhere on the basis of a misdiagnosis of hyperthyroidism. The corrected diagnosis was nervous tension and exhaustion in 112 cases; menopause, 30; physical exhaustion, 27; normal, 11, colloid goiter, 11; rheumatic endocarditis, 3; psychoneurosis, 8; hypothyroidism, 6; and miscellaneous, 20. It was believed that in the first or largest group the most important single factor was the excessive use of coffee, tea, and tobacco, often used in very large amounts that were sufficient to explain the nervous tension, tremor, insomnia, cardiovascular disorders, and weight loss.

Correlation Between Clinical Severity and Function Tests

Schultz & Zieve (44) have examined the relationships between the clinical severity of hyperthyroidism and the results of thyroid function tests. Using a battery of tests to evaluate the degree of hyperthyroidism in individual patients, it was found that all the information available was at times inadequate to reach an accurate conclusion. Nevertheless, if one were to use two tests, the thyroidal I^{131} clearance and the basal metabolic rate (BMR) were the most accurate guides in predicting clinical severity. The correlation between clinical severity and the estimated weight of the thyroid gland was of the same magnitude as that between clinical severity and the BMR. The best single correlation was that for the thyroidal clearance of I^{131}. The serum protein-bound iodine level was less precise in indicating the level of hyperthyroidism than one might wish However, it is to be remembered that both the conversion ratio (reflecting the rate of conversion of radioactive iodine to organically active iodine in thyroid hormones) and the serum protein-bound iodine level are affected not only by the rate of hormone formation *but also by the rate of peripheral utilization*

It was concluded that the function tests all represent relatively inexact reference points by which to compare patients as to severity of hyperthyroidism Clinical appraisal remains the best means of comparing severity among individuals or groups, but the tests obviously afford important supporting data.

The fairly frequent association of hyperthyroidism with osteoporosis, increased urinary excretion of calcium, and an accelerated turnover of calcium stores has been again emphasized by Epstein *et al* (10). They point out, however, that hyperthyroidism is not usually seriously considered in the differential diagnosis of hypercalcemia, and that only four cases have been recorded in which hypercalcemia was believed to be a consequence of the hyperthyroid state. A patient is reported in whom hyperthyroidism was associated with hypercalcemia, nephrocalcinosis, and renal insufficiency. *With successful treatment of the hyperthyroidism, the hypercalcemia disappeared* and renal function improved considerably.

and in suppression of the radioiodine uptake. Roentgenograms revealed regression of chest metastases.

THE PARATHYROID GLANDS

Brisk interest continues in the detection and management of hyperparathyroidism. It is widely appreciated that many cases of hyperparathyroidism are diagnosed late, if ever, and that calcium and phosphorus determinations must be performed in all patients who have signs and symptoms which might suggest the condition. Health can be completely restored if the diagnosis is made early enough and surgical excision of the hyperfunctioning tissue, the only effective therapy, performed.

CLINICAL SYNDROMES MET IN HYPERPARATHYROIDISM

Incidence of bone and renal lesions—There is increasing realization that the symptomatology and pathophysiology of hyperparathyroidism are more far-reaching and generalized than had previously been appreciated. In reviewing the clinical findings in 207 cases studied at the Mayo Clinic between 1928 and 1954, Black (2) found that 12 per cent had osseous complications, 82 per cent combined osseous and urinary or urinary alone, and 6 per cent demonstrated neither osseous nor urinary complications Among the 6 per cent were backache, polyendocrine adenomas, adenoma found during thyroidectomy, tumor of the mandible, adenoma found at necropsy, and aching of the muscles. It will be noted, however, that the above series ended in 1954. During the last seven years, certain other important manifestations of hyperparathyroidism have been more clearly perceived and utilized in the diagnosis and management of these patients

Abdominal symptoms.—Thomas *et al* (49) have emphasized that hypercalcemic crisis results from hyperparathyroidism Acknowledging that the first detected cases of hyperparathyroidism were those with generalized bone disease and next, those with renal calculi, these workers point out that more recently it has been recognized that there are patients in whom gastrointestinal symptoms are predominant and that these include nausea, vomiting, and abdominal pain The purpose of their communication is to emphasize the hypercalcemic crisis which may occur with the symptom complex of intractable nausea and vomiting, progressive drowsiness, and coma These symptoms usually develop in association with a high serum calcium concentration and may be associated with a decreasing urine volume, a rising serum phosphorus, and progressive azotemia. Of three patients studied with this syndrome, an emergency removal of the parathyroid adenoma resulted in a successful outcome in two In the third patient, the correct diagnosis was suspected only 2 hr before death In such patients, the physicians may be led to explore the abdomen in the mistaken belief that even pyloric or intestinal obstruction may be present.

Hyperparathyroidism, pancreatitis, and peptic ulcer—Another clinical concept or perception which is assuming increasing prominence in surgical thought is the association between primary hyperparathyroidism, pan-

had already died. It was again borne out that there is a contralateral spread in many patients not only from one thyroid lobe to the other but from the right lobe, for example, to lymph nodes on the opposite side. Total thyroidectomy was considered indicated in all patients with thyroid cancer—regardless of whether or not the individual operator should find sufficient indications, from his point of view, to perform a radical neck dissection on the involved side and perhaps later on the opposite side. In their series, 50 per cent of the patients had cervical metastases on admission, 18.7 per cent having bilateral metastases.

The general management of tumors of the thyroid was also considered by Ward (50). He advocates most strongly that when proved carcinoma of the thyroid is present, one should do a total thyroidectomy and, in most instances, perform a radical neck dissection on the primary side. Again, the present writer agrees that, if there is biopsy evidence of lymph node involvement or extension of the tumor from the thyroid gland, then *en bloc* radical *neck dissection should be performed, in the present state of knowledge* While available hormonal therapy can be suppressive, it certainly is going to cure very few cancers.

Medical Management of Thyroid Cancer

Moore (38) and Thomas (48) have recently reported upon the further use of thyroid hormone to suppress the growth of thyroid cancer, presumably by way of the pituitary gland with suppression of the secretion of TSH by that organ The first author calls attention to the reciprocal relationships which may exist between the pituitary and other endocrine glands, called "biologic feedback" mechanisms. One of the most striking examples of such relationships exists between the pituitary and the thyroid, not to mention that which exists between the pituitary and the adrenal cortex. In the presence of an environmental deficiency of iodine and inadequate thyroxine formation, the pituitary responds by increasing the release of TSH further to stimulate the thyroid, resulting not infrequently in the development of adenomas of this target organ Evidence of pituitary hyperplasia has been *demonstrated in the presence of thyroid deficiency, and the administration* of thyroid substance to patients with adenomatous goiter will often reduce the size of the goiter, presumably by depressing the secretion of thyrotropin (TSH). Moreover, various workers have reported beneficial effects of thyroid substance upon the size of thyroid metastases Moore reports a case in which large doses of thyroid resulted in spectacular regression of many advanced skeletal and soft tissue metastases.

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measurement of pituitary gland suppression The response of thyroid cancer seemed to be similar to that observed when other means of pituitary inhibition are employed. Ten patients were studied. The administration of *L-triiodothyronine* resulted in a fall in the serum protein-bound iodine level

Phosphate clearance.—Kyle and his associates (31) have emphasized that [illegible] sufficiently marked in many [illegible]

subjects, the mean phosphate clearance measurement during the forenoon under fasting conditions was 10.8 ± 2.7 ml /min. Except in one patient with associated severe renal disease, the phosphate clearance was substantially elevated in hyperparathyroidism. In 10 patients with parathyroid deficiency, the phosphate clearance was significantly depressed, even when the hypo-

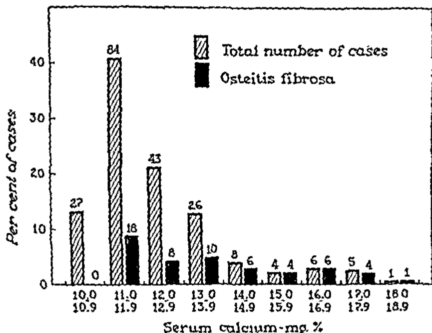


FIG 2. Serum calcium levels in hyperparathyroidism Note that the level was below 12 mg per 100 ml. in 84 of 207 consecutive cases (2).

calcemia was corrected by vitamin-D_2 therapy. They concluded that the measurement of phosphate clearance is a valuable screening test for hyperparathyroidism and is of diagnostic aid in parathyroid deficiency.

The changing diagnostic criteria for hyperparathyroidism have also been reviewed by Goldman *et al.* (15). Recognizing that the accurate chemical screening of patients with nephrolithiasis, nephrocalcinosis, acute hypercalcemia, or skeletal disorders has resulted in the recognition of more patients with the disease, they sought an even more precise test for the

creatitis, and peptic ulcer. The association between pancreatitis and hyperparathyroidism was emphasized by Cope *et al.* (6). They described two cases and collected five others from the world literature. Subsequently, Hoar & Gorlin (22) have reported an additional case of hyperparathyroidism and acute pancreatitis. In their case, admitted with abdominal pain which was diagnosed as acute pancreatitis and was associated with an elevated serum amylase level, the suspicion of hyperparathyroidism was raised on the second hospital day when a serum calcium level was found to be 7.5 m eq./l. (normal, 5.5 m.eq.). The serum calcium level had been ordered because a lowered level would have indicated the formation of large amounts of calcium soaps, reflecting presumably a more serious degree of pancreatitis. The elevated level, quite unexpected, indicated hyperparathyroidism, and a parathyroid adenoma was successfully removed.

In speculating upon the possible mechanism by which hyperparathyroidism can lead to pancreatitis, these authors mentioned the known fact that excessive parathyroid hormone can cause focal pancreatic necrosis. As an alternative explanation, it was also pointed out that calcium can be precipitated in the ductal system of the alkaline-secreting pancreas, resulting in obstruction to flow of exocrine secretion. The stones tend to disappear from the ducts, and pancreatitis does not usually recur after ablation of the overactive parathyroid tissue. Whether unsuspected pancreatitis accounts for many of the cases of abdominal pain in patients with hyperparathyroidism is not known.

The association of hyperparathyroidism and peptic ulcer (40) is now well recognized and is generally accepted as one of the more rare manifestations of primary hyperparathyroidism. In such cases, it is far preferable, of course, to detect and remove the parathyroid adenoma than to do a gastric resection for the peptic ulcer, since the latter may be expected to subside following adequate surgical management of the hyperparathyroidism.

Diagnosis of Hyperparathyroidism

Serum calcium levels.—Although it has been emphasized above that the symptomatology of hyperparathyroidism may range from the pain of bone cyst or renal stones to that of pancreatitis or peptic ulcer or even clinical evidence of alimentary obstruction, the diagnosis of a parathyroid adenoma or of the much more rare hyperparathyroidism caused by hyperplasia of one or more of the glands finally rests upon chemical determinations of the serum and phosphorus levels, along with the measurement of the excretion of these ions in the urine. Moreover, since hypercalcemia has come to be the finding most often associated in physicians' minds as the essential criterion for the diagnosis or proof for the existence of hyperparathyroidism, it is of particular importance to emphasize that this hypercalcemia may be mild indeed. For example, in the previously mentioned series of 207 cases reviewed by Black (2), 84 cases had serum calcium levels which ranged from only 11.0 to 11.9 mg. per 100 ml. This represented slightly more than 40 per cent of the cases (Fig. 2).

had been carried out previously elsewhere. Thus, opening the mediastinum is necessary in not more than 0.5 to 1 per cent of cases.

Postoperative care.—In the usual case, the values for calcium and phosphorus in blood and urine revert to normal within a day or so In some cases, on the other hand, the concentration of phosphorus may remain depressed for weeks, this being particularly true in cases of osteitis fibrosa cystica. It is assumed that the phosphorus is here being used for skeletal repair There may also develop, along with a markedly elevated alkaline phosphatase level, a type of tetany called "bone-hunger tetany." In contrast to the mild transient tetany which may occur in about 50 per cent of cases without osseous disease, where no treatment is usually required, these patients with bone-hunger tetany may require intensive treatment which includes intravenous injection of calcium in huge quantities. The tetany persists until recalcification of the skeleton is well advanced. It is usually possible to control symptoms fairly well by the intravenous administration of calcium lactate and by giving calcium and AT_{10} or vitamin D by mouth.

Prognosis—Hyperparathyroidism resulting from adenoma or hyperplasia does not usually recur, certainly not often. On the other hand, malignancies of the parathyroid glands do occur, and the treatment is usually disappointing. The lesion tends to recur locally and eventually metastatic lesions may appear elsewhere Death may occur from uncontrollable hyperparathyroidism and its complications, rather than from the carcinoma itself.

The skeletal changes manifested in osteitis fibrosa cystica may be expected to disappear On the other hand, gross deformities may persist, and true bone cysts will not recalcify The pain and tenderness in the bones usually disappear very quickly after the operation, long before the skeleton has had time to recalcify to a degree discernible on x-ray.

Actually, the prognosis of this condition resides largely in the status of renal function at the time the hyperfunctioning tissue is diagnosed and successfully removed. If renal function remains at a satisfactory level, the prognosis is excellent. On the other hand, if far advanced renal damage has been allowed to occur because of calcinosis or actual stone formation in the kidney with surrounding infection, the patient may still succumb later, even though the parathyroid adenoma has been removed.

THE THYMUS GLAND

Various types of tantalizing evidence suggest that the thymus gland is an endocrine organ. Soutter *et al* (47) have reported a series of 13 thymomas and have described the different histologic pictures encountered. Seven of the tumors were classified as malignant on the basis of anaplasia or local invasion. These authors bring out the fact that approximately 30 per cent of thymomas are associated with myasthenia gravis, though the results of resection of the tumor are variable with respect to the effect on the myasthenia gravis itself. Nine cases of thymoma, all malignant, have been found to be associated with Cushing's syndrome, and hypoplastic anemia has been found associated with 16 cases. Acquired agammaglobulinemia has been en-

diagnosis of hyperparathyroidism in patients whose hypercalcemia is minimal. In contrast to the previously emphasized hypophosphatemia, the serum phosphate levels in their patients had been normal in most of the recent cases of surgically proved hyperparathyroidism. The tubular reabsorption of phosphate measured by a simplified technique was uniformly subnormal in their patients with hyperparathyroidism. They felt that this test was of diagnostic value in those patients with the minimal hypercalcemia and normal phosphate levels

Primary hyperparathyroidism associated with hypomagnesemia.—Pointing out that conclusive evidence of a clinical syndrome related to a deficiency of magnesium in man is lacking, Agna & Goldsmith (1) described three patients with proved adenomatous hyperparathyroidism who demonstrated clinical abnormalities believed to be related to magnesium deficiency. The clinical symptoms and signs in two of the patients, findings which were ascribed to hypomagnesemia, subsided in association with magnesium sulfate therapy. The role of magnesium in normal and abnormal human metabolism was briefly reviewed.

Treatment of Hyperparathyroidism

It is again emphasized by Black (2) that the only known treatment of hyperparathyroidism is the removal of the lesion or lesions of the parathyroid glands. The technical problems have to do largely with the widespread positions in which the parathyroids may be located, and with the minute size of many of the adenomas. More than one gland may be involved, and thus it is necessary to identify all four glands routinely. It is also important that a competent pathologist be available to recognize from frozen section tissue the normal, atrophic, and hypertrophic parathyroid tissue. Fortunately, more than 90 per cent of the parathyroid glands are situated in the immediate vicinity of the thyroid or within 3 cm below the inferior poles, and in the majority of cases the location of the glands is remarkably constant. The superior glands are located so far medially that they are more properly described as lying on the hypopharynx than on the thyroid. The inferior glands are located more laterally and anteriorly. Mediastinal parathyroids are usually closely associated with the thymus, and they may be located within the gland.

Parathyroid adenoma rarely in mediastinum—Black feels strongly that the cervical dissection, which is always carried out first, should not be followed by a mediastinotomy at the same operation It is again emphasized that normal or atrophic parathyroid glands should not be removed prior to the detection of the adenoma, lest hypoparathyroidism be produced after removal of the adenoma. (There is a great temptation to remove this one or that one because it appears to be a little larger than a parathyroid previously exposed.) Regarding the frequency of the presence of the parathyroid adenoma in the mediastinum, Black found that in the more than 250 proved cases at the Mayo Clinic only three mediastinotomies had been necessary to find and remove the adenoma, and in two of these cervical explorations

which led to careful study for the possibility of intracranial pathology, in particular, a tumor. The history, which extended over seven years, consisted of recurrent episodes of disturbed consciousness with amnesia and automatism, reminiscent of the symptoms of temporal lobe dysfunction. The attacks did not occur in the fasting state, and the fasting blood sugar levels were never below 60 mg./100 ml. Nevertheless, the attacks were relieved by partial pancreatectomy. Although the patient had been free of the attacks for approximately one year following surgery, the author wisely was cautious in pronouncing cure. It has been repeatedly reaffirmed that when an islet cell adenoma is not found in the resected specimen following partial pancreatectomy for hyperinsulinism, it may be found in the residual pancreas at autopsy. Hyperinsulinism is almost invariably a result of adenoma and most rarely is it caused by adenomatosis of the islets of Langerhans.

In the liver, the action of glucagon is on the enzyme phosphorylase. On activation of phosphorylase by glucagon, glycogen breakdown occurs. The infusion of glucagon continuously can markedly reduce the liver glycogen stores. Glucagon has been found to counter experimental insulin-induced hypoglycemia.

Ulcerogenic tumors of the islets of Langerhans.—Zollinger & McPherson (54) have reviewed the evidence for the relationship between a nonbeta cell adenoma of the islets and marked hypersecretion of acid with a malignant type of peptic ulcer diathesis. Approximately 48 cases of this syndrome have now been recorded, and the triad consisting of fulminating ulcer diathesis, marked gastric hypersecretion, and associated nonbeta islet cell tumor of the pancreas should be looked for in ulcer patients with markedly elevated gastric acid formation. A primary jejunal ulcer is especially suggestive of the presence of such a tumor.

The exact mechanism by which the tumor may produce the gastric hypersecretion and ulceration has not been determined Both the cell type and an active principle must be identified to confirm or deny the relationship between these tumors and gastric hypersecretion.

Donaldson *et al.* (8) report an additional case of the Zollinger-Ellison syndrome with a review of the literature, pointing out that multiple endocrine tumors are often found in the presence of the gastric hypersecretion and hyperacidity. In addition to the islet cell adenoma, these include pituitary tumors, parathyroid adenomas, and adenomatosis of the adrenal glands. The islet cell adenoma associated with the Zollinger-Ellison syndrome rarely secretes insulin. Peptic ulceration is not common in association with the usual islet cell adenoma, composed of beta cells which produce the well-known hyperinsulinism.

THE ADRENAL GLANDS

The Adrenal Cortex

In current surgical practice, the three major problems involving the adrenal cortex are (*a*) the degree and length of cortical atrophy following prolonged corticosteroid therapy for medical diseases; (*b*) the proper manage-

countered in four cases of thymoma. In concluding their report of their own cases and a review of the literature, these workers point out that the frequent development of malignancy in thymomas is considered an indication for their removal, where possible. The sensitivity of some thymic tumors to radiation and to hormonal therapy is offered as an alternative when adequate surgery is impossible (which it frequently is). Finally, the effect of thymectomy upon myasthenia gravis is unpredictable, upon Cushing's syndrome it is harmful, and in hypoplastic anemia it is often helpful

The surgery of the thymus gland has also been discussed by Child & Donovan (4). Cognizance is taken of the insecure position of the thymus as a respectable member of the endocrine family, but they feel that there is sufficient evidence of an hormonal function of this organ, although as yet unidentified, to justify fully its inclusion among the endocrine organs. The enlargement of the thymus in adult life is usually discovered on routine roentgen examination of the chest because of signs and symptoms of a tumor in the anterior mediastinum, or because a patient manifests stigmata of myasthenia gravis. They, too, point out that the relationship between thymic abnormality and myasthenia gravis is far greater than can be accounted for by chance. This has given rise to the belief that the overactive thymus releases some as yet unidentified curarelike substance. Among the characteristics of myasthenia gravis when associated with a tumor (instead of with the hyperplasia which often occurs earlier in life) are its severity, its more rapid course, and the greater difficulty with which it is controlled.

Thymectomy: pre- and postoperative measures.—Any patient with a known or suspected thymoma should be studied preoperatively with great care to detect evidence of neuromuscular disease. Morphine, barbiturates, and cu-

tinued postoperatively until it is assured that an acute myasthenic crisis is not going to develop. The best results of thymectomy for myasthenia gravis are achieved when thymectomy is performed early in the course of the disease.

THE PANCREAS

It has been arbitrarily decided to omit discussion of pancreatitis, pancreatic carcinoma other than that affecting the islets of Langerhans, pancreatic pseudocysts, etc. Thus, the discussion is limited to pathology involving endocrine functions of the islets of Langerhans. The problems which most interest us here are those having to do with hypoglycemia caused by hyperinsulinism, the antagonistic effect of glucagon administration (11) in

in the world. The patient had psychiatric manifestations with each attack,

stimulation of the adrenal gland, as would be the case where the pituitary is secreting excessive amounts of this trophic hormone, can result in a transformation of adrenal hyperplasia to adrenal carcinoma The question is not settled, but cases are cited in which apparently non-neoplastic adrenals had been visualized at operation many years prior to the development of a tumor. The authors caution against the failure to treat virilism caused by adrenocortical hyperplasia with suppressive hydrocortisone therapy, lest hyperplasia develop into neoplasia.

Diagnosis of Cushing's syndrome.—The clinical features of Cushing's syndrome are generally acknowledged to be a result of an excessive secretion of the adrenocortical steroids, usually by hyperplastic adrenals There is still disagreement, however, as to whether the fundamental derangement resides in the hypothalamus, the anterior pituitary, or in the adrenal cortices themselves Most workers feel that the anterior pituitary, stimulated by way of the hypothalamus, may be the chief offender, in that it elaborates increased amounts of ACTH. Furthermore, total adrenalectomy can abolish most of the features of the syndrome, though in recent months there has been an increasing awareness that tumors in the pituitary itself may be *responsible for certain of the features that have previously been associated* with some cases of Cushing's syndrome, features which may continue as a result of the pituitary tumor after both adrenals have been removed.

The diagnosis of Cushing's syndrome in borderline cases is often quite difficult. Therefore, the recent demonstration that patients with this condition show a characteristic abnormality in the response of the plasma 17-hydroxycorticosteroid level to the administration of ACTH has been a useful finding. (Incidentally, it has been pointed out that this hyper-responsiveness of the adrenal cortex could be interpreted as evidence suggesting that an intrinsic adrenocortical disease may be the basic lesion. That is, if the adrenal cortex is abnormally sensitive to ACTH, the Cushing's syndrome might be produced in the presence of a normal amount of ACTH which had an unusually great effect upon the secretory cells of the adrenal cortex, which were unduly sensitive to the trophic hormone) Christy *et al* (5) and Geller *et al.* (13) have related their experiences with the adrenal responsiveness to corticotropin in normal subjects and in patients with Cushing's syndrome The suppressive effect of prednisone has also been examined and described In brief, Christy *et al* found that the exaggerated response to ACTH of the adrenal cortex in Cushing's syndrome, associated with bilateral adrenocortical hyperplasia, was confirmed in 14 of 15 patients with the disease The excessive response persisted after unilateral adrenalectomy Moreover, in contrast to normal subjects, the excessive adrenocortical response in six patients with bilateral adrenal hyperplasia proved relatively resistant to suppression by the administration of prednisone, a finding which was at variance with that in normal subjects. There was suggestive evidence, on the basis of limited data, that in patients with adrenal hyperplasia, who experienced clinical remissions following pituitary radiation, the adrenocortical response to ACTH reverted toward normal In three patients who

ment of Cushing's syndrome; and (*c*) the management of adrenal virilism. There is also continued interest in the use of bilateral adrenalectomy in the management of patients with metastatic carcinoma and certain other conditions However, the results of the use of adrenalectomy for hypertension have been disappointing, and it has probably now had an adequate trial.

Adrenalectomy for Nonadrenal Conditions

Giuseffi *et al.* (14) have investigated the use of bilateral adrenalectomy in a patient with massive ascites and postnecrotic cirrhosis. Since evidence had indicated the presence of an abnormal sodium and water retention in patients with hepatic ascites, they determined to try this procedure in a 28-year-old man. A striking increase in urinary sodium excretion was evident postoperatively while the patient was on maintenance cortisone therapy. The significant defect in sodium and water excretion, presumably independent of aldosterone, persisted postoperatively. A progressive loss of ascites occurred while the patient was ingesting approximately 100 m.eq of sodium per day, and appeared to be the result of both the hypoaldosteronism and the diminished fluid-retaining abnormality. The experience with this case was felt sufficiently favorable to warrant further investigation of adrenalectomy for the management of ascites.

Adrenalectomy for Metastatic Cancer of the Breast: Evaluation and Five-Year Follow-up

Results.—Dao & Huggins (7) performed adrenalectomy in 52 patients with metastatic mammary cancer. There were 2 postoperative deaths. Objective remission of varying duration followed in 12 of 32 patients who had bilateral adrenalectomy alone, and in 8 of 18 patients who also had oophorectomy. There was little correlation between the extent of the metastatic lesions and the results of surgery, for two patients with metastases so extensive that one appeared moribund, survived for more than five years with great regression of the neoplastic process. On the basis of experience thus far, four criteria are advanced for selecting the patients most likely to be helped by adrenalectomy: (*a*) age between 40 and 65 years; (*b*) indications of slowness of neoplastic growth, (*c*) a high titer of estrogenic substances in the urine; and (*d*) a rather well-differentiated appearance of the breast tumor as seen under the microscope. There was no evidence that simultaneous oophorectomy helped in women older than 54 years. The fact that [illegible] of time occurred in 20 of the 52 [illegible] these findings, it has been the [illegible] hat it is impossible to predict which patients will be materially benefited by adrenalectomy for far advanced mammary cancer.

Cushing's Syndrome

Does adrenocortical hyperplasia result in adrenocortical carcinoma?—The question is raised by Hamwi *et al.* (16) as to whether long-continued ACTH

not be maintained, apparently because of a severe and prolonged inhibition of endogenous ACTH production.

Management of hyperadrenocorticism.—The surgical therapy of tumors of the adrenal cortex has been considered by Raker (41) and by Heinbecker *et al.* (20). In general, surgical thought at the present time is concerned with whether or not a subtotal or a total adrenalectomy should be performed for Cushing's syndrome caused by hyperplasia. A tumor should, of course, be removed. As stated previously, however, the vast majority of cases of both Cushing's syndrome and the adrenogenital syndrome result from hyperplasia. Tumors causing either syndrome are likely to be malignant. Many surgeons, the writer included, are unwilling to perform total adrenalectomy in Cushing's syndrome, where a radical subtotal adrenalectomy will produce a normal level of adrenal activity in most patients. If the right adrenal is removed *in toto* and but a remnant spared on the left side, this remaining tissue is easily found if a second operation is required, for one can trace the central adrenal vein as it enters the left renal vein. Recurrence is not very common. By this more conservative approach to the excision of adrenal tissue, the patient is not rendered permanently "Addisonian" when medical measures may become available for the more effective suppression of adrenocortical activity in Cushing's syndrome. Certainly, the use in recent years of corticosteroid therapy to suppress the androgen production in adrenal virilism caused by hyperplasia has given rise to genuine hope that similar therapy may become available for Cushing's syndrome resulting from hyperplasia. At the present time, however, surgical excision of the hyperfunctioning tissue is mandatory in Cushing's syndrome.

In the case of adrenal virilism (pseudohermaphroditism, adrenogenital syndrome) arising from hyperplasia, the condition is usually managed by the administration of cortisone or hydrocortisonelike compounds. If, with hydrocortisone therapy, the urinary excretion of 17-ketosteroids fails to decline to a normal level in the patient with virilism, the condition may be caused by a tumor and the abdomen should be explored. Again, the possibility that a pituitary tumor is present should not be excluded, even though most of the signs resulting from the adrenal hyperactivity disappear. The patient should be followed with frequent visual field examinations.

Sobel *et al.* (46) have reported the use of hypophysectomy for the control of functioning metastases, following initial removal of an adrenal carcinoma. The excision of the pituitary gland was only temporarily effective, however, and the urinary excretion of 17-ketosteroids rose again within one week.

The Adrenal Medulla: Pheochromocytoma

A detailed clinical experience with nine cases of pheochromocytoma has been recorded by Lance *et al.* (32). Pheochromocytoma is probably more prevalent than is generally believed; manifestations are paroxysmal in nature in only slightly more than 50 per cent of patients; an increased use of urinary catechol amine determinations should render the diagnosis of

did not improve clinically after pituitary radiation, the adrenocortical response remained excessive. Thirteen patients who were severely ill from nonadrenal disease and who exhibited no physical evidence of adrenocortical hyperfunction, exhibited responses to ACTH which were quantitatively similar to those occurring in the patients with bilateral adrenal hyperplasia. In 5 of 6 patients with Cushing's syndrome caused by adrenocortical adenoma or carcinoma (rather than to hyperplasia), the exaggerated plasma hydroxycorticosteroid response to ACTH did not occur.

Mechanism of adrenal atrophy in Cushing's syndrome caused by adrenal tumor.—Atrophy of the contralateral adrenal gland is a characteristic feature of Cushing's syndrome resulting from an adrenal tumor. Furthermore, this type of adrenal hypofunction is of major importance in that the adrenal atrophy associated with the administration of adrenocortical hormone therapy (Fig. 3) may be caused by similar and perhaps identical mech-

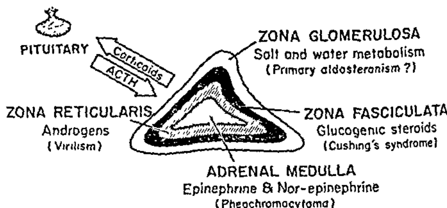


FIG. 3. The adrenal cortex represents, in effect, three endocrine organs in one. A reciprocal or feedback mechanism exists between the hydrocortisonelike steroids and the pituitary secretion of ACTH. The zona glomerulosa is largely independent of pituitary control (From Hardy, J D, *Pathophysiology in Surgery*, The Williams and Wilkins Co., 1958.)

anisms. It has been appreciated for some years that cortical atrophy can be effectively reversed, at least temporarily, by the administration of ACTH. However, in a case reported by Kyle *et al.* (30), hypoadrenalism persisted following resection of the tumor until three separate courses of ACTH stimulation had been given, the last almost two years following operation. In another patient, the features of hypoadrenalism were even more intense. The atrophic adrenal gland was repeatedly stimulated with ACTH, but on each occasion hypoadrenalism rapidly recurred after cessation of the exogenous ACTH stimulation. It was concluded from these studies that although the adrenal atrophy may be reversed by ACTH, this reversal may

Testicular tumors in children.—Phelan *et al.* (39) have studied testicular tumors in children They include a report of nine cases and a review of the literature (464 cases). Teratomas of the testis in children appear to be relatively benign tumors Embryonal carcinomas are highly malignant, and seminomas and chorionepitheliomas in infants and children are pathologic rarities.

The Ovary

The endocrinologic potentialities of certain tumors of the ovary are well known, and little has been published that is new The granulosa cell tumor produces feminization in prepubertal children and postmenopausal bleeding in the elderly. The arrhenoblastoma produces virilism at any age. Israel & Mutch (25) have reviewed and classified feminizing tumors and masculinizing tumors. Smith (45) has called attention to the fact that a few unexpectedly good outcomes may be achieved in the treatment of ovarian cancer.

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the condition more satisfactory than it has been with the use of often hazardous pharmacologic "provocatory" tests. It is exceedingly hazardous to perform any other operation upon a patient who has a pheochromocytoma, for the tumor should always be managed first except in the most unusual circumstances. The adequate and intelligent use of adrenolytic drugs during surgery increases the margin of safety significantly. Others (19) have re-emphasized the relationship between pheochromocytoma and neurofibromatosis, and a pheochromocytoma of the urinary bladder has been reported (43). Masson *et al.* (35) have described a diagnostic procedure for pheochromocytoma which utilizes a technique of assay of urine in the rat and the demonstration of piperoxan hydrochloride antidiuresis during the normotensive phase. Plasma catechol amine levels are often helpful.

THE TESTIS AND OVARY

The Testis

Tumors of the testis constitute a small segment of the malignant lesions met in the male (about 1 per cent) (33). Delay in surgical excision is often a result both of reluctance on the part of the patient to consult his physician, and of failure of the latter to appreciate the true significance of the testicular swelling. The pathologic pictures encountered are varied. Primary tumors of the testis may be divided into three groups: (*a*) those arising from the germ cells; (*b*) those arising from the cells of Leydig (interstitial cell tumors); and (*c*) those arising from connective tissue cells (Sertoli cell tumors, fibromas, etc.). Tumors arising from the germ cells comprise about 95 per cent of the total. Seminomas account for from 40 to 50 per cent of all tumors of the testis, and the average age of patients is about 30 years. Embryonal carcinomas comprise about 20 per cent of all testicular tumors, and the average age of onset is somewhat lower than that for seminoma. Teratomas and teratocarcinomas account for about 30 per cent of testicular tumors All three tumors metastasize to the retroperitoneal lymph nodes, but may also exhibit blood-borne metastases.

Diagnosis.—Testicular tumor is most often diagnosed when a patient presents with testicular swelling. Other conditions such as hernia, hydrocoele, epididymitis, or gumma may be confusing. One should not biopsy the testis, according to Leadbetter (33). If a diagnosis cannot be made by external examination, an inguinal incision should be made, the inguinal canal opened, the spermatic cord freed, and the cord occluded with a rubber-shod clamp at the inguinal ring The testis is then gently freed, the tunics incised and the testicle inspected. If it is incised, great care should be taken to avoid spillage of tumor cells

A 24-*hr.* urine specimen should be tested quantitatively for urinary follicle-stimulating hormones. If elevated, this finding is of value in serving as a baseline in following the patient for recurrences, after treatment with orchiectomy, retroperitoneal lymph node dissection, and deep roentgen therapy.

Testicular tumors in children.—Phelan *et al* (39) have studied testicular tumors in children. They include a report of nine cases and a review of the literature (464 cases). Teratomas of the testis in children appear to be relatively benign tumors. Embryonal carcinomas are highly malignant, and seminomas and chorionepitheliomas in infants and children are pathologic rarities.

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ALLERGY AND IMMUNOLOGY[1,2]

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The knowledge of allergy and immunology is expanding rapidly in many different directions, varying from fundamental studies of the formation and action of antibodies to practical methods of the treatment of allergic diseases. The total number of significant contributions in each calendar year is too great for adequate review in the space allotted here. Because of the large amount of material and the uneven progress in different areas of the subject, most of the reviewers of recent years have felt that the space available could be more advantageously used by an adequate coverage of a few interesting subjects rather than by attempting to cite briefly each contribution of the year to the entire field. The establishment of this precedent makes its continuation almost necessary, since the discussion of subjects not covered for several years cannot logically be limited to the material appearing in one year. This chapter is therefore confined to a few subjects in which notable progress has recently been made, chiefly related to clinical and experimental allergy, rather than to general immunology.

Mechanism of anaphylaxis.—Notable advances have been made in elucidating the mechanisms of anaphylactic shock. In general, these have been consistent with the view of Dale (1) and others (2), that the physiologic changes in anaphylaxis are the results of the release by antigen-antibody reaction of autopharmacologic agents present but previously bound in an inactive form in tissues or blood constituents. However, studies of the reaction in various species of animals show great differences in the relative importance of the various pharmacologically active substances or "tissue hormones" (2) involved. The more important and best-characterized of these agents are histamine, acetylcholine, serotonin (5-hydroxytryptamine), and heparin; others are bradykinin (3), "substance P" (4), and the slow-reacting substance SRS-A (5, 6).

Anaphylaxis in the guinea pig appears to result largely from release of histamine by the antigen-antibody reaction This species is highly sensitive to injected or inhaled histamine and the symptoms produced by it are essentially identical with those of anaphylactic shock If the lungs of sensitized guinea pigs are perfused with Ringer's solution, addition of the specific antigen to the perfusion fluid causes the release of measureable amounts of histamine (7). Analysis of the circulating blood of the intact animal during anaphylaxis shows the presence of concentrations of histamine adequate to

[1] The survey of the literature pertaining to this review was completed in August, 1958.

[2] The following abbreviations will be used. DNA (deoxyribonucleic acid); L.E. (lupus erythematosus); RNA (ribonucleic acid).

produce the symptoms (8), and the chief effects of anaphylactic shock in the guinea pig are inhibited by adequate doses of antihistamine drugs (9).

Mongar & Schild have studied in detail the release of histamine from sensitized guinea pig lung by antigen. Most of the histamine contained in the cells is bound to the mitochondria. When the antigen is added to a suspension of minced lung (consisting largely of intact cells) from a sensitized guinea pig, histamine is released from cells to the supernatant fluid. If the cells are then broken down mechanically, the mitochondria and other cell fragments are found to be depleted of histamine (10). However, if the sensitized cells are homogenized into particles and antigen is then added, no histamine is released. The antigen releases histamine only from intact, living cells (11). The release of histamine by antigen requires energy (12) and is inhibited by oxygen lack, iodoacetate, phenol, and such metabolic depressants as phenylbutazone and amidopyrine (13). On the contrary, release of histamine by histamine liberators, such as 48/80 and octylamine, does not require energy or intact cells, and is unaffected or even increased by oxygen lack, iodoacetate, and phenol. When antigen is added in the presence of phenol and the release of histamine blocked, the cells are desensitized, indicating that the antigen-antibody reaction has taken place, but subsequent physiologic changes are inhibited. If the phenol and antigen are washed out within 3 min., release of histamine may subsequently occur without further addition of antigen, the mechanism started by the antigen-antibody reaction continuing if the inhibitor is quickly removed.

The release of histamine by antigen is also shown to depend on the presence of calcium ions and to be stopped by versene. Potassium and magnesium are without effect (14). The release is optimal at pH 7.8 and decreases rapidly as the hydrogen ion concentration is changed in either direction. The effect of temperature is also striking (15). Histamine is released by antigen only in the range of 20° to 45°C. with a sharp maximum between 35° and 40°C. The inhibition by low temperatures is reversible; heating at 45°C produces an irreversible change in regard to release of histamine by antigen, but does not affect release by octylamine. This is not caused by destruction of the complement, which is relatively stable up to 50°C. Mongar & Schild also note that sensitized smooth muscle heated a few minutes at 45°C loses its reaction to antigen and its release of histamine on exposure to antigen, but when returned to 37°C still reacts to exogenous histamine. The curves relating the release of histamine by antigen to temperature and to pH resemble those of enzyme systems.

On the basis of these observations, Mongar & Schild (13) believe that the antigen-antibody reaction initiates in the living cell an active physiologic reaction requiring oxygen and energy, which releases histamine. They hypothesize that a preformed enzyme percursor is activated into an enzyme which releases bound histamine. The active enzyme is believed to be unstable and to remain active only a few minutes. Inhibition by heat above 45°C. is believed to destroy irreversibly the enzyme precursor, phenol in-

inhibits the active enzyme, with the effect reversible during the brief life of this enzyme. Regardless of these hypothetical details it is apparent that a complex active process is involved; histamine does not escape simply as a result of nonspecific damage to the cell Release of histamine by 48/80 and octylamine, on the other hand, appears to be a chemical reaction in which the cell is passive. The existence of a complex enzymatic mechanism for the release of histamine by antigen suggests that it serves some purpose in normal physiology. The nature of any such function is unknown

Mongar & Schild (13) concluded that in the guinea pig lung the mechanisms of release of histamine by antigen and by histamine liberators (48/80 and octylamine) were quite different. However, McIntyre (16), in extensive studies of histamine release from rabbit platelets, found a closer relationship between the specific release by antigen and the nonspecific release by histamine liberators. He noted that slight changes in the chemical structures of the simple histamine releasers produced compounds which inhibited the release These compounds not only inhibited the release of histamine by small molecular releasers, but also the release by specific antigen-antibody reactions.

*Geiger, Hill & Thompson (17) studied the effects of a variety of pharma*cologically active agents on the Schultz-Dale reaction of the guinea pig ileum. They found that cyanide, azide, fluoride, fluoroacetate, and dinitrophenol had no effect on the reactions to antigen, histamine, or acetylcholine. Iodoacetate, which (as noted above) inhibits the release of histamine from the guinea pig lung by antigen, inhibited the reaction of the ileum to antigen but not to histamine or acetylcholine Aging the tissue had a similar effect. Ganglionic blocking agents had no effect on the reactions to antigen, histamine, or acetylcholine Botulinum D toxin, believed to inhibit postganglionic nerve fibers (18), blocked the reaction to antigen, but only variably affected that to histamine and had no blocking effect on that to acetylcholine. The evidence that postganglionic nerve fibers may be involved in the reaction to antigen is further discussed by Geiger & Alpers (19)

While histamine is apparently the principal autopharmacologic agent released in anaphylaxis in the guinea pig, it is not the only one. Kellaway & Trethewie (5) in 1940, reported the presence in perfusates of the anaphylactic guinea pig lung of a "slow reacting substance" which produced contractions of the guinea pig ileum persisting longer after the bath was washed than those caused by histamine. Brocklehurst (20) showed that in prolonged perfusion of the anaphylactic guinea pig lung, the smooth muscle-stimulating activity of the effluent collected during the first 5 min. was caused almost entirely by histamine, while fractions collected later contained a slow reacting substance which caused contraction of the guinea pig ileum despite high concentrations of atropine and the antihistamine, mepyramine (Neoantergan) It was also shown to contract human bronchial muscle in the presence of atropine and mepyramine By biologic tests it was found to be distinct from serotonin, bradykinin, and substance P It was apparently identical

with the slow reacting substance of Kellaway and Trethewie, and Brocklehurst designated it SRS-A.

The possible role of serotonin in anaphylaxis has attracted considerable attention. This compound, like histamine, has the effect of stimulating smooth muscle and increasing capillary permeability. Both effects are most marked in rats and mice, but they are also apparent in rabbits, guinea pigs, and other species. Fink (21) found that in stimulating the uterus of the mouse, serotonin was 1000 times as active as histamine (to which the mouse is relatively resistant). In the guinea pig, on the other hand, Herxheimer (22) found that serotonin administered by aerosol was only half as effective as histamine in producing bronchospasm. Sparrow & Wilhelm (23), observing the effect on permeability of skin capillaries, found serotonin 25 times as potent as histamine in the rat, but the two compounds were of essentially equal activity in guinea pigs and rabbits. Parrot & West (24) also found serotonin far more potent than histamine in producing permeability of the rat skin capillaries.

While serotonin is widely distributed in the body, particular interest in relation to anaphylaxis is attached to its presence in mast cells, platelets, and lung. The rat and mouse, which are particularly susceptible to the smooth muscle and capillary permeability effects of serotonin, also demonstrate remarkably high concentrations of it bound in their mast cells (25, 26). In this respect they differ from most other species studied, including man, guinea pig, rabbit, dog, cat, hamster, and cow (27, 28). Humphrey and his associates (29, 30) showed the presence of serotonin in the platelets of a variety of animals, in concentrations generally exceeding that of histamine. They showed that dog platelets absorbed free serotonin from solution and suggest that this may be a normal mechanism of controlling the plasma level of free serotonin. They also reported that the platelets of man, cat, and ferret contained an unidentified third substance which stimulates smooth muscle in the presence of the inhibitors of serotonin and histamine. Weissbach, Waalkes & Udenfriend (31) demonstrated that serotonin was present in the lungs of rats, mice, and rabbits in concentrations of approximately 2 μg./gm while the lung of the guinea pig contained only one-tenth as much, but relatively more histamine. Humphrey & Jaques (32) found that the reaction of antigen and antibody *in vitro* caused the release of serotonin from rabbit platelets suspended in plasma. They showed that the actual quantity of serotonin released was about three times as great as that of histamine, the release of which had been described by previous workers

Since the mouse is strikingly resistant to the effects of injected histamine, and antihistamine drugs are relatively ineffective in protecting them against anaphylactic shock, it appears doubtful that histamine plays a significant role in the reaction in this species. Mayer (33) has questioned whether the tissues of the mouse contain enough preformed histamine to produce anaphylactic shock On the other hand, the mouse is highly susceptible to the effects

of serotonin; its tissues contain adequate amounts to produce the reaction, and the effects of anaphylactic shock are inhibited by the known antagonists of serotonin, reserpine and chlorpromazine (34). When antigen is injected into the sensitized mouse, the tissue mast cells immediately lose their characteristic granules which are believed to be associated with the bound serotonin (35). Fink (36, 37) has also shown that in stimulation of the isolated mouse uterus, serotonin is 1000 times as active as histamine, and that the Dale reaction in the uterus of the sensitized mouse was specifically inhibited by the known antagonists of serotonin, lysergic acid diethylamide (LSD) and reserpine, but not by diphenyl hydramine hydrochloride (Benadryl hydrochloride). Furthermore, *Hemophilus pertussis* vaccine, which is known to make mice more susceptible to anaphylaxis, also renders them more susceptible to serotonin. In certain strains of mice, Munoz & Greenwald (38) found that pertussis vaccine increased susceptibility to both serotonin and anaphylaxis, but did not affect the reaction to histamine. While the mechnism of anaphylaxis in the mouse is not entirely proved, it appears probable that serotonin plays a prominent role and histamine is of little importance.

The mechanism of anaphylactic shock in the rabbit has long presented problems. Compared to the guinea pig, the rabbit is quite resistant to anaphylactic shock and relatively large amounts of antigen must be injected intravenously to produce the reaction. The occurrence of shock is manifested by a drop in peripheral blood pressure, secondary to obstruction of the pulmonary circulation, which has been generally attributed to spasm of the pulmonary vessels. Katz (39) demonstrated the release of histamine from the blood of sensitized rabbits when antigen was added *in vitro*. However, actual measurements by Rose & Weil (40) of the blood histamine of rabbits during anaphylactic shock showed a decrease, in contrast to the increases noted in the guinea pig and dog by Code (8).

Waalkes *et al.* (41) found that the levels of both histamine and serotonin in the plasma of rabbits rose sharply but briefly during anaphylactic shock. The level of serotonin reached a peak in 1 min. and that of histamine in 2 min., both falling abruptly within 3 min. On the other hand, the whole blood content of both serotonin and histamine fell sharply during the first 2 min. because of a rapid decrease in the platelet content. Whether these transitory changes in the plasma content of the pharmacologicaly active agents actually play a significant role in the course of anaphylaxis is not clear.

Coca (42) noted in 1909 that when sensitized rabbits were shocked with nucleated blood cells, the pulmonary vessels were so blocked with masses of nucleated corpuscles that death might be attributed to embolism. However, he was inclined to consider that the more important change was spasm of the walls of the blood vessels of the pulmonary circulation (43).

The occurrence of amorphous material believed to be thrombi in the pulmonary capillaries of rabbits dying in anaphylactic shock has been noted by Vaubel (44) and others (45, 46). Dixon (47), using antigens labelled with

I-131, noted that these "thrombi" contained considerable concentrations of radioactive antigen, suggesting that they were antigen-antibody precipitates occurring within the vascular system.

Germuth and his associates (48) studied this problem by the use of fluorescent antigens. By the injection of specific and unrelated fluorescein-labelled proteins, they showed clearly that the masses of amorphous material in the pulmonary capillaries of shocked rabbits were specific antigen-antibody precipitates. Injection into the veins of normal rabbits of antigen-antibody precipitates formed *in vitro*, was shown to produce symptoms identical with those of anaphylactic shock. On the other hand, injection into rabbits of soluble antigen-antibody complexes (capable of causing anaphylactic shock in guinea pigs), caused no significant reaction. These authors suggest that the embolization of pulmonary vessels by specific antigen-antibody precipitates is a major cause of the circulatory failure which is the principal feature of anaphylactic shock in the rabbit, but do not exclude the possibility of other mechanisms

This explanation of the pathogenesis of anaphylactic shock in the rabbit has appeal because of the lack of direct evidence of an adequate autopharmacologic mechanism, the relatively large amounts of antigen required to produce shock in this species, the large amounts of antibody required to produce passive sensitization, and the necessity for intravenous injection of antigen to produce shock. It should be noted that similar emboli are not present in man or guinea pig succumbing to anaphylactic shock.

Passive cutaneous anaphylaxis.—While the immediate reversible wheal and erythema type of skin reaction is a familiar manifestation of human allergy, the best known skin reaction of experimentally sensitized animals is the hemorrhagic Arthus phenomenon However, Zinsser (49) described, in 1921, transitory edematous reactions following injection of antigen into the skin of sensitized guinea pigs. The production of similar lesions in passively sensitized guinea pigs was reported by Dienes (50) and by Ramsdell (51, 52). These reactions, while analogous to the urticarial response of human skin, lack the sharply defined wheal and surrounding erythema. They are therefore less conspicuous than the reactions of human skin and require close observation, but Chase (53) utilized them in the study of sensitization to simple chemical compounds. Ramsdell (51) pointed out that the rather inconspicuous and transitory lesions could be made obvious and persistent by injecting a dye such as trypan blue intravenously and simultaneously with the antigen It is this procedure which has been reviewed by Ovary (54) under the name of passive cutaneous anaphylaxis

Following the usual technique, the antibody is injected intracutaneously, the antigen and dye together injected intravenously 3 to 6 hr later. Ovary (54) states that as little as 0 0003 μg of rabbit antiovalbumin antibody nitrogen produces a positive reaction in guinea pig skin when a large excess of antigen is used The reaction can also be elicited by intravenous injection of antibody and subsequent intracutaneous injection of antigen, but the amount of antibody required for this method is much larger (30 μg.) and

essentially the same as needed for induction of passive general anaphylaxis in the guinea pig.

The former procedure is one of the most sensitive methods available for detection of antibody. Fischel and his associates (55) injected cells removed from actively sensitized guinea pigs into the skin of normal guinea pigs and reported that they were able to detect the antibody produced by one to five million spleen cells. When the cells were removed from the donor guinea pigs within the first week after the sensitizing injections, the time required for passive sensitization of the skin varied from 12 hr. to 3 days, being longer in cases where the cells were removed early. Hydrocortisone had no measureable effect on the reaction.

This type of passive sensitization is readily produced in guinea pigs with rabbit and guinea pig antisera, but not with horse or goat antisera. The results obtained with various types of human antisera are of special interest. Ovary & Biozzi (56) obtained positive reactions with human sera containing antibodies for *Eberthella typhi* and *Bacillus melitensis*, and also with both precipitating and nonprecipitating human tetanus antitoxin. Fisher, Middleton & Menzel (57) reported positive reactions with sera of human patients convalescent from serum sickness induced by equine tetanus antitoxin, but negative with the sera of persons "spontaneously" allergic to horse serum who had never received injections of this antigen With the sera of hay fever patients, Ovary (54) found some positive reactions, others negative, despite the fact that the latter sera gave strongly positive Prausnitz-Kustner reactions in human skin Fisher and his associates (57, 58) found uniformly negative results with sera of hay fever patients, as well as with those of patients "spontaneously" allergic to other antigens Negative results were obtained also with the sera of nonsensitive volunteers given injections of ragweed pollen to induce the formation of blocking antibodies, and with the sera of patients allergic to penicillin which produced a Prausnitz-Kustner reaction in human skin

Fisher & Cooke (58), on the basis of their own observations and those of Ovary & Biozzi (56), conclude that the activity of human antisera in producing passive cutaneous anaphylaxis in the guinea pig is closely related to its ability to produce general anaphylaxis and the Dale reaction in the same species With a few exceptions, the active sera also contained precipitating antibodies There was no relationship between activity in passive cutaneous anaphylaxis in the guinea pig and the Prausnitz-Küstner reaction in human skin.

The histology of the reaction has been described by Biozzi, Mene & Ovary (59) and by Fisher & Cooke (58) The lesions produced by means of small amounts of antibody resemble those caused by intracutaneous injection of histamine, involving the capillaries and venules rather than the arterioles, which are characteristically affected by the Arthus reaction (60). With larger amounts of antibody, the lesions show the arteriolar spasm and hemorrhagic features of the Arthus phenomenon

The physiologic mechanism of the reaction is still unsettled and, like

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findings in guinea pigs. Schild and his associates (69) demonstrated that the excised bronchial muscle of the asthmatic human contracted on addition to the water bath of the specific antigen and on addition of free histamine. The reaction to histamine was readily inhibited by mepyramine, but the reaction to antigen was only partly inhibited by high concentrations of the drug. As in the sensitized guinea pig lung, perfusion with antigen caused release of measureable amounts of histamine.

Subsequent studies by Brocklehurst (70, 71) showed that when the excised lung of an asthmatic human was perfused with Tyrode's solution containing the specific antigen, the effluent fluid contained both histamine and SRS-A. As in the guinea pig lung, most of the activity of the fluid during the first 5 min. was caused by histamine, while in samples collected after 30 min., 70 per cent was attributable to SRS-A. The two active substances were separated by adsorption on charcoal and elution with aqueous butanol. The SRS-A from human lung appeared to be identical with that from the guinea pig. The relative inefficacy of antihistamine drugs in controlling the contraction of isolated human asthmatic bronchial muscle exposed to antigen seen by Schild *et al.* (69), agrees with the clinical impression that antihistamines are only partially effective in bronchial asthma. In the past this has been explained on the basis of local concentrations of histamine released within or on the surface of the muscle cell, or to the action of intrinsic histamine at sites not reached by the antihistamine drugs. However, the presence of a second pharmacologic agent not affected by antihistamine drugs appears to offer a far more satisfactory explanation.

The relationship of serotonin to human bronchial asthma remains uncertain. In several reported cases of functioning carcinoid tumors which secrete large amounts of serotonin, symptoms suggestive of bronchial asthma have been noted (72, 73). Page (74) attributes these manifestations to the bronchoconstrictor effect of serotonin which is readily demonstrated in the cat (75) and guinea pig (72). Lesions of the heart valves are a prominent feature of the majority of such cases (76), but these lesions are predominantly right-sided, lessening the probability that the dyspnea noted can be attributed to cardiac asthma.

However, the more direct evidence offers less support to the view that serotonin is a bronchoconstrictor in man. Herxheimer (77) reported that four normal humans were not affected by inhalation of 0 67 per cent aerosol of serotonin which produced severe bronchospasm in guinea pigs. In three of six asthmatic patients, inhalation of the serotonin aerosol produced asthmatic attacks, which later studies (78) indicated were probably related to the irritating effects of the acid solution. When the same concentration of serotonin was inhaled in an aerosol buffered to pH 7 there was no effect on three asthmatic patients, including one who had previously reacted to the unbuffered material. Brocklehurst (6) reported that the effect of serotonin on isolated human bronchial muscle was one of slight relaxation rather than contraction.

Direct chemical measurements of free serotonin in the blood or body

that of systemic anaphylaxis, may well vary in different species. In the guinea pig, Ovary (54) found that the effects of minute amounts of antibody were inhibited by antihistamine drugs, but with larger amounts of antiserum, even large doses of antihistamine drugs produced only partial inhibition. In the rat, Brocklehurst, Humphrey & Perry (61) found that antihistamine drugs were ineffective as inhibitors. Possibly the transitory reaction of passive cutaneous anaphylaxis, which is produced in some instances by nonprecipitating antibody, may depend on the release of various autopharmacologic agents, while the Arthus reaction, requiring large amounts of precipitating antibody (62), may involve formation of antigen-antibody precipitates in the tissues. Further studies are needed to elucidate the relationship between the two types of response.

Physiologic mechanism of human allergy.—The similarity between the more violent allergic reactions of humans and experimental anaphylactic shock is obvious. While the antibodies involved in the two types of reaction differ in that precipitates are usually present in anaphylaxis and not in human allergy, it is often assumed that the physiologic mechanisms initiated by the antigen-antibody union are similar. In view of the varying physiology of anaphylactic shock in different species of experimental animals, this concept requires clarification. In so far as the physiologic mechanisms of human allergy have been established, they appear to resemble those of anaphylaxis in the guinea pig more closely than those in the rabbit, mouse, or other species studied.

The evidence against histamine as an important intermediary product in human allergic disease has been summarized by Roche e Silva (2). General acceptance of this concept is reflected in the widespread use of antihistamine drugs, which are notably effective in hay fever and urticaria, but less so in bronchial asthma.

Further evidence of the involvement of histamine in the production of urticarial wheals is offered by the marked exacerbations induced in subjects susceptible to the disease by injections of the histamine liberator L-1935 (63, 64). After the bodily store of preformed histamine was depleted by one or more injections of the histamine releaser, remissions occurred which could be prolonged by the administration of cortisone, apparently by inhibiting the formation of new histamine.

The release of histamine from the cellular constituents of the blood into the plasma, when the specific antigen was added to the whole blood of hay fever patients, was described by Katz & Cohen (65) in 1941, and further studied by Noah & Brand (66, 67) Recent studies reported by Middleton *et al.* (68) have shown that this phenomenon, in many respects, closely resembles the release of histamine from sensitized guinea pig lung described above. Histamine release from human blood cells is also inhibited by versene and other calcium binding agents, by phenol, and by iodoacetate, but is not affected by a number of other well-known enzyme inhibitors.

Studies of bronchial and lung tissue excised (because of other disease) from patients with bronchial asthma have also shown close parallels to the

tion of antibody, (*b*) "univalent" nature of the antibodies, without the multiple combining groups necessary to form an aggregate with antigen; or (*c*) the nature of the antigens, pollens in particular being relatively poor antigens when injected into experimental animals. Until recently, little direct evidence has been available to support any one of these explanations.

The skin-sensitizing antibody is demonstrated only by the Prausnitz-Küstner phenomenon, the amount present in a serum or serum fraction being measured by the highest dilution which shows a distinct reaction. While the urticarial reaction in human skin is a specific and sensitive indicator of antigen-antibody reaction, it depends upon a complex physiologic mechanism whose activity varies in different normal skins, so that the same amounts of sensitizing serum and antigen may react quite differently in various persons. While comparisons made simultaneously on the skin of the same individual measure the relative amounts of antibody in two sera or serum fractions, absolute endpoints are of little quantitative significance (82) The determination of blocking antibody in the method devised by Loveless (182) depends on the comparison of the effects of blocking and control sera on the Prausnitz-Kustner reaction in the same test subject, so the effect of these variations in different subjects is less important. However, all methods based upon passive transfer involve the practical difficulties of securing suitable human volunteers and the risk of transmitting infectious diseases, particularly homologous serum virus hepatitis For these reasons, considerable attention has been devoted to attempts to develop *in vitro* methods for distinguishing and measuring skin-sensitizing and blocking antibodies

Studies of the sera of untreated allergic patients in complement-fixation by Gyorgy, Moro & Witebsky (91) and, more recently by Cavelti (92), showed some positive results but the reactions were weak, inconstant, and not correlated with activity in the Prausnitz-Kustner reaction Sensitization of whole blood of hay fever patients is readily demonstrated *in vitro* by the release of histamine when the specific antigen is added, but this method does not distinguish between cellular and plasma reactivity (65) In some cases, the presence of antibodies in the sera of allergic patients has been demonstrated by the passive sensitization of normal human blood *in vitro* and subsequent release of histamine by antigen, but consistent results have not been obtained by methods developed so far (68).

Demonstration of blocking antibodies *in vitro* has been more successful. Hampton *et al* (93, 94) found that sera of human patients treated with ragweed pollen inhibited the precipitation of ragweed antigen and rabbit antiragweed serum Portnoy & Sherman (95) demonstrated inhibition of the complement-fixation reaction of ragweed antigen and rabbit antiragweed serum by the sera of treated hay fever patients. This activity was related to the titer of blocking antibody as measured by the classical method on human skin, but the *in vitro* method was less sensitive than that of passive transfer Follensby (96) has shown the difficulty of applying the various *in vitro* methods to the practical determination of blocking antibodies

fluids of asthmatic patients are not available. Berg & Westermeyer (80) studied the excretion of 5-hydroxyindole acetic acid, the principal product of serotonin catabolism, in the urine of asthmatic patients during attacks and during free intervals. Rather surprisingly, the excretion was less during the attacks. The explanation of this change was not apparent, but there was no evidence of increased serotonin excretion and breakdown during the active stage of asthma. Pending further direct measurements, it appears premature to assume that serotonin plays an important part in human allergic disease.

Antibodies in human allergy.—The application of immunologic methods to the study of the common allergic diseases, hay fever and extrinsic asthma, has been hampered by the fact that the sera do not contain precipitating antibodies and fail to produce passive sensitization in the common laboratory animals (79) The presence of antibody in the sera of untreated patients is manifested by the passive local sensitization of normal human skin, the Prausnitz-Küstner phenomenon (81), the factor in the serum producing this reaction being known as the skin-sensitizing antibody or reagin. After conventional treatment of the patient with injections of antigen, the serum contains a second antibody for the same antigen, the blocking or thermostable antibody which is distinct from the sensitizing antibody, lacking skin-sensitizing activity but inactivating the specific antigen so that its reactions with the sensitizing antibody are inhibited The older information concerning the properties of these skin-sensitizing and blocking antibodies has been reviewed elsewhere (82).

Briefly, the skin-sensitizing antibody is generally present in the sera of untreated and treated patients; it is characterized by a marked affinity for the skin and mucosa where it remains fixed for periods as long as two months, it fails to pass through the intact placenta from maternal to fetal circulation, and loses its skin-sensitizing properties when heated at 56°C. In the case of skin-sensitizing diphtheria antitoxin, Kuhns & Pappenheimer (83) have shown that sensitizing antibody which has lost skin-sensitizing activity through heating, retains its ability to react with antigen and becomes essentially a blocking antibody. Such a change has not been observed in the sera of untreated hay fever patients, the blocking antibody is demonstrable only in the sera of patients treated with injections of antigen The skin-sensitizing antibody is not easily localized in serum globulin components separated by electrophoretic or alcohol precipitation methods. Activity has been found to be associated with gamma (84, 85), beta (86, 87) and alpha-2 (88) fractions separated by various methods

The blocking antibody produced in both allergic and nonallergic persons by injections of antigen is stable at 56°C., permitting its separation from skin-sensitizing antibody (88). It shows less affinity for tissues and readily passes the placental barrier In electrophoresis it, like most antibodies, is essentially limited to the gamma globulin fraction (89, 90)

The failure of the sera of either untreated or treated patients to show precipitin activity has been attributed to: (*a*) lack of an adequate concentra-

gave positive reactions, while 67 per cent of sera from treated patients were positive. They noted that heating sera 4 hr. at 56°C. did not greatly affect the hemagglutination reaction. In several cases the titer was somewhat higher with heated serum but probably within the limits of error of the method. Arbesman and his co-workers (108) reported an untreated case of extreme allergy to mouse dander and serum, in which hemagglutination was demonstrable by both the Boyden and *bis*-diazotized-benzidine techniques, the highest titer being obtained with tanned cells coated with mouse serum. They also noted that hemagglutinating activity persisted when the skin-sensitizing activity of the serum was destroyed by heat.

Gordon, Rose & Sehon (109, 110), using rabbit erythrocytes linked to ragweed pollen by the *bis*-diazotized-benzidine method, obtained high titers and found consistently positive reactions with the sera of both untreated and treated patients which gave positive Prausnitz-Küstner reactions; the reactions were positive also with the sera of nonallergic volunteers who had received injections of ragweed pollen. The hemagglutination titers showed some relationship to the titers of skin-sensitizing antibody; those of the treated patients were only slightly higher than those of untreated patients. When active sera were absorbed with large amounts of antigen-coated cells, titers of hemagglutinating, blocking, and skin-sensitizing antibodies were reduced correspondingly. The hemagglutination reaction was specifically inhibited by the addition of soluble antigen to the system. When serum was fractionated by zone electrophoresis, the hemagglutinating activity was found in the same fractions as the skin-sensitizing antibody. Heating serum for 11 hr. at 56°C., which completely destroyed its skin-sensitizing activity, did not affect the hemagglutination.

These results indicate that divalent (multivalent) antibodies capable of forming aggregates of antigen-coated particles are present both in the sera of untreated patients, which contain skin-sensitizing antibody, and the sera of nonsensitive persons receiving antigen injections which contain blocking antibodies The use of rabbit antihuman globulin serum to produce aggregates is unnecessary. The observation that absorption with antigen-coated cells removes all three types of antibody activity from the serum suggests that the hemagglutination is caused by the same antibodies producing skin-sensitization and blocking. The greater sensitivity of the *bis*-diazotized-benzidine method, as compared to the tanned cell method, is apparently caused by the firmer bonds binding antigen to the cells and less inhibition by escape of free antigen into solution. The retention of hemagglutinating activity by the sera of untreated patients when the skin-sensitizing activity is destroyed by heat is not considered proof that a different antibody is involved, since the actual mechanism of this thermolability is unknown Possibly there may be an effect analogous to that observed by Kuhns & Pappenheimer (83), who showed that skin-sensitizing human diphtheria antitoxin lost its property of passively sensitizing skin after being heated but still reacting with antigen, becoming, in effect, a blocking antibody.

Follensby & Lowell (97) have shown that ragweed blocking antibody, when precipitated with rabbit antihuman gamma globulin serum, retains the property of combining with ragweed antigen, so that a suspension of such precipitate absorbs antigen from ragweed solutions. The decrease in antigenic activity was demonstrated in tests on sensitized human skin, but appears to be susceptible of test by *in vitro* methods using rabbit anti-ragweed sera. This phenomenon, incidentally, offers confirming evidence that the blocking antibody is gamma globulin.

In recent years, many attempts have been made to demonstrate antibodies in the sera of allergic patients, before or after treatment with injections of antigen, by agglutination of antigen-coated particles. In 1941, Cohen & Weller (98) reported the agglutination of ragweed-coated collodion particles by the sera of hay fever patients, particularly those who had received treatment. However, Swineford & Houlihan (99) were unable to confirm these findings.

In later efforts, Boyden's method (100) of adsorbing antigen on the surface of tanned erythrocytes has been utilized. In order to detect "univalent" antibodies, Coombs, Howard & Mynors (101) suggested the procedure of exposing antigen-coated cells to human allergic sera with subsequent agglutination by rabbit antihuman globulin. The coupling of antigen to red cells by the *bis*-diazotized-benzidine method of Pressman, Campbell & Pauling (102), as modified by Stavitsky & Arguilla (103), has also been utilized.

Orlans, Rubinstein & Marrack (104), using the Boyden technique with cells coated with timothy pollen, found hemagglutination with 8 of 22 sera from untreated hay fever patients, two of which reacted in relatively high dilutions Sera of 15 patients fully treated with pollen injections all showed positive reactions, ten in dilutions higher than in any of the untreated patients. Britton & Coombs (105), by the same method, found no reactions with the sera of 11 untreated hay fever patients, while approximately half of the patients who had received injection treatment showed agglutination These authors studied the same sera by the red cell-linked antigen method of Coombs, Howard & Mynors (101) and found a higher percentage of reactions in both groups By this technique all of the treated patients showed positive reactions and a majority of the untreated reacted in low titers Since all of the human sera used were heated for one-half hour at 56°C, the authors considered it unlikely that the antibody causing agglutination in sera of untreated patients was the thermolabile skin-sensitizing antibody. The greater agglutination by rabbit antigamma globulin sera of cells exposed to sera of treated as compared to untreated patients may perhaps be related to the electrophoretic findings that blocking antibody is gamma globulin, while skin-sensitizing activity is not limited to this fraction of the serum globulins.

Feinberg, Davison & Flick (106, 107), using the Boyden method, found that 21 per cent of sera from untreated grass or ragweed hay fever patients

plex mixtures of several antigens, and not suitable for immunochemical methods. The determination of blocking antibodies in passive transfer (119) and even in clinical treatment (120) are affected by the presence in ordinary ragweed extracts of multiple antigens, at least two of which are important in hay fever.

Attempts to separate and characterize these antigens, initiated by Caulfield *et al.* (121) in 1935, have since been made in a large number of laboratories The earlier studies were reviewed by Newell in 1941 (122), who noted that the total allergenic activity was caused by several substances of complex chemical nature; some were proteinlike substances of relatively low molecular weight while others were largely carbohydrate.

Stull and his colleagues (*123, 124, 125*) separated, by chemical methods, two water-soluble fractions of different antigenic specificity from low ragweed pollen, both of major importance in clinical allergy, as well as a third water-soluble fraction which is apparently of less clinical significance. Rockwell described five biologically active fractions differing in carbohydrate content and solubility in acid solutions (126, 127).

Abramson *et al* (128 to 132) employed a variety of chemical, electrophoretic, and ultracentrifugal methods to separate a major, slow-moving, unpigmented component, trifidin, from giant ragweed, and the corresponding compound, artefolin, from low ragweed. The two compounds were found to be quite similar and to have molecular weights of about 5000 They also noted the presence of about six distinct minor components in the pollen of each species

Danker *et al* (133) and Perlman (134) separated by paper chromatography, six and ten components, respectively, which differed in their reactions in skin tests on various ragweed allergic patients.

Becker & Munoz (135), using the Oudin gel diffusion technique with rabbit antiserum, demonstrated the presence of five distinct antigens in ragweed pollen. Wodehouse (136), using the Ouchterlony technique, found seven distinct bands when low ragweed pollen extract was diffused against rabbit antiserum. Occasionally an eighth was discernible. Many of the minor antigens were dialyzable, and may have been formed by breakdown of the major components. Cebra (137), using the Preer (138) modification of the Oudin method, also found seven or eight bands of precipitation with low ragweed pollen extract. Wodehouse (139) has attempted to correlate the bands noted in gel diffusion with the antigens separated by other workers using chemical, chromatographic, and electrophoretic methods, which suggests that Abramson's artefolin, Stull's fraction 1, and Rockwell's major antigen are identical and correspond to his antigen C.

Goldfarb and his co-workers (142) have continued the study of trifidin and have also applied a method of solvent precipitation to giant ragweed. They found evidence of five antigens but, on the basis of a relatively few intradermal tests on allergic patients, were inclined to consider only one of importance in clinical hay fever.

While these findings help to clarify the nature of the antibodies of allergic sera, the various hemagglutination methods used do not permit distinction between, and separate *in vitro* measurements of, the skin-sensitizing and blocking antibodies which are clinically and immunologically of quite different significance Techniques which do not produce hemagglutination with sera of untreated patients also fail to show reaction with a considerable number of sera from treated patients. Sera of occasional untreated patients may show hemagglutinating activity as great or greater than treated patients (108).

The skin-sensitizing and blocking antibodies were further characterized by the studies of Sehon *et al* (111, 112) by ultracentrifugation of sera from allergic patients. They found that the skin-sensitizing antibody moved with the rapidly sedimenting globulin fraction (sedimentation constant 18–20) while the blocking antibody was associated with the bulk of the gamma globulin (sedimentation constant 6–7) While certain other antibodies, namely Wassermann antibodies (113), Rh antibodies (114), antithyroid autoantibodies (115), and the agglutinating factor in rheumatoid arthritis (116), have been related to the fast-sedimenting globulin, most ordinary antibodies are present in the slower moving globulins The difference is consistent with the somewhat bizarre characteristics of the skin-sensitizing antibody: development without unusual antigen exposure, tissue affinity, placental filtration, thermolability, and electrophoresis, in all of which respects the blocking antibody shows the usual behavior of acquired antibodies. It is in accordance with the idea that skin-sensitizing antibodies represent the reaction of a congenitally abnormal immune mechanism to natural exposures to antigen while the blocking antibody is the normal response to antigen injections.

Pollen antigens —Aside from the nature of the antibodies involved, the greatest obstacle to the immunologic study of human allergies has been the lack of pure well-characterized antigens. None of the hundreds of antigen extracts used routinely in the clinical diagnosis and treatment of allergic disease is a pure antigen by immunochemical standards The long, careful study by Stevens, Spies & Bernton [see Coulson in (117)] of the cottonseed antigens has shown the difficulty of isolating pure antigens even from allergenic materials readily available in unlimited quantities Studies by Vaughan & Kabat (118) have shown that the allergenic activity of relatively pure materials such as recrystallized egg albumin may be greatly affected by traces of impurities Isolation and definition of the antigens contained in natural materials active as allergenic agents is therefore an important step in the study of allergic disease

Most of the studies of human allergy made in America have utilized patients with ragweed hay fever because of the frequency and clinical importance of the condition. The pollen is readily available and antigenic solutions suitable for clinical skin tests and treatment are easily prepared by extraction with water or saline solutions. These crude extracts are com-

decreased, and that the formation of blocking antibody may be enhanced by an adjuvant effect. Actually, the first use of such extracts by Sutton (152) in 1923 antedated the concepts of adjuvants and blocking antibody. The principle was further applied by Naterman (153) who, in 1938, suggested the use of antigens emulsified with lanolin and oil, and later, in 1951 (154), introduced a preparation in which the pollen antigen was first precipitated with tannic acid and then suspended in peanut oil with aluminum monostearate. With this material he reported 90 per cent good results in 111 patients, a shortened course of treatment, and relatively few general reactions. However, persistent nodules at the sites of injection and two sterile abscesses were noted. Malkiel & Feinberg (155), using a suspension of antigen in sesame oil with aluminum monostearate, considered their results poor and the incidence of general reactions not decreased.

Loveless (156) has used suspensions of antigens in mineral oil, corn oil, and isopropyl meristate (Deltyl) with Falba as an emulsifying agent. The course of treatment was shortened to three to five injections given in one day. Her results were similar to those of Naterman (154), the clinical benefits being essentially equal to those obtained by conventional treatment, although the change in the objective conjunctival test was somewhat less. The incidence of general reactions was 3 per cent in the group treated with mineral oil suspensions, and 18 per cent with the meristate antigen. Nodules produced by the mineral oil suspensions persisted as long as six years, but no abscesses or tumors resulted.

Brown (157), employing the same materials and methods, reported that the incidence of general reactions could be greatly reduced by administering epinephrine and antihistamine drugs before and for two days after the treatment. Brown's clinical results both in ragweed (158) and tree hay fever (159) were somewhat less satisfactory than those expected from the usual injection treatment. This method is interesting because of the great reduction in the number of visits required for treatment. However, this radical shortening of the treatment has outweighed the possible lessening of general reactions which might be expected from a slowly absorbed antigen. The evaluation of clinical results in the treatment of hay fever is always difficult, and from the reports now available it appears that further study employing careful statistical methods is needed before it can be considered for routine use.

Immunologic responses to insulin.—Since the insulin used in the treatment of diabetes is heterologous protein derived chiefly from bovine and porcine sources, it is not surprising that occasional patients show immunologic reactions to repeated subcutaneous injections. These responses are most commonly manifested by urticarial allergic reactions Less frequent, but often affecting the same patients who show urticarial sensitization, is the development of resistance to the physiologic effects of exogenous insulin, manifested by insulin requirements considerably in excess of those of the depancreatized man, often over 200 units per day. The sera of patients

Sehon, Rose and their associates (140, 141) as well as Cebra (137) applied the method of starch zone electrophoresis to the separation of ragweed antigens. Sehon and Rose found evidence of at least two fractions of importance in ragweed hay fever. They indicated the inadequacy of skin tests on allergic patients as measures of the activity and specificity of fractions, and outlined a method of desensitizing passively sensitized sites as an indication of antigenic specificity. While these studies do not permit final conclusions, it appears that satisfactory understanding of the relationships and significance of the antigens will depend on separating the various components into sufficient quantities to permit detailed chemical and immunologic studies.

Grass pollens, which are the chief cause of hay fever in Europe and second only to ragweed in America, have received less study. Abramson *et al.* (143) separated seven allergically active components from timothy pollen by electrophoresis. Augustin (144, 145, 146) reported the separation from timothy pollen of albumin and globulin fractions, both active in skin tests on allergic patients, nondialyzable, and with molecular weights estimated to be 14,000. In agar diffusion tests by the Oudin method, she found that most common British grass pollens contained one main component which was antigenically similar in all The main antigenic component precipitated by rabbit antisera was shown to be active in skin tests on hay fever patients.

Using the Ouchterlony method, Wodehouse (147) studied the antigens of the pollens of six common American grasses timothy, redtop, June, sweet vernal, orchard, and Bermuda grass. In each species there was one major component and six or eight minor bands. The principal component appeared to be antigenically identical in all of the specimens studied except Bermuda grass, which was completely different in specificity. This close antigenic relationship between grasses of different genera is supported by previous studies using many other methods (148, 149, 150)

By the same methods, Wodehouse (151) studied the antigenic relationship between the pollens of different weeds of the Amaranthaceae and Chenopodaceae families Four species of the amaranth family, careless weed, pigweed, spiny amaranth, and Western water hemp, were tested against rabbit anticareless weed serum All were found to contain essentially the same antigens in similar proportions, suggesting that they might be considered together in allergic testing and treatment On the other hand, five species of Chenopodaceae, Russian thistle, burning bush, lambs quarters, shadscale, and annual saltbush, showed distinctly different antigens, indicating that each genus must be considered separately.

Repository treatment of hay fever. During the past year, interest has been revived in the use of pollen antigens suspended in oils for the treatment of hay fever. These antigen preparations are more slowly absorbed than the conventional aqueous extracts and are used with the expectation that fewer injections will be required to produce the same clinical benefit, that the incidence of general allergic reactions due to overdoses of antigen may be

120 to 200 units daily and four doses of 70 to 90 units Of nine patients giving negative results, one had received 100 units, four, smaller doses, and four, no insulin.

Silk antigen in biological products.—Allergic reactions to immunizing agents have frequently been reported in the past, particularly those of egg-sensitive patients to virus and rickettsial vaccines produced by cultures in egg yolk. Some reactions to tetanus toxoid, which does not contain egg antigens, have been shown to be due to peptones used in the culture medium (169), but the nature of the antigen in other cases was obscure (170). Particularly perplexing are patients who suffer severe allergic reactions from a variety of different and apparently biologically unrelated immunizing agents, or from homologous materials such as human gamma globulin (171). Coleman (172) noted ten such patients, five previously reported (173, 174, 175), and five unreported, in which the reactions were traced to silk antigen present in the biologic products as a result of silk filters used in their preparation. Reactions occurred after the use of combined diphtheria, pertussis and tetanus, plain tetanus toxoid, typhoid vaccine, and human gamma globulin. Some of the patients reacted similarly to two or more of these materials, but often failed to react to the same agent prepared by another manufacturer. All of the patients were shown to be highly allergic to silk by direct or passive transfer tests The biologic products producing the reactions were found to have been passed through silk filters at some stage of preparation, and were shown to give reactions in the patient's skin or in passive transfer tests, while similar products obtained from manufacturers not using silk filters did not Passive transfer tests with the serum of one patient (172) gave reactions to certain reputable brands of typhus, cholera, influenza, mumps, poliomyelitis, and catarrhalis combined vaccines; crude liver extract and vitamin B-12 produced similar responses, suggesting contamination of all of these products by silk filters The use of silk filters by pharmaceutical manufacturers is reportedly being curtailed. However, caution appears to be warranted in the injection of any biologic material into patients known to be highly allergic to silk. The danger of reaction does not depend upon the biologic nature of material being injected, but only on the use of silk filters in its preparation, so the results may vary with different brands of the same agent. A preliminary skin test with the actual preparation to be used is advised as the best precaution for avoiding reactions

Immunologic factors in lupus erythematosus.—Since the autoimmune diseases were reviewed by Dixon in the previous volume of this series, important additions have been made to the evidence for an autoimmune mechanism in disseminated lupus erythematosus It is well known that the sera of many or most patients with systemic lupus contain a gamma globulin capable of inducing *in vitro* the formation from normal leucocytes of the Hargraves' L.E cell which is characteristic of the disease. Holman & Kunkel (176) showed by starch electrophoresis that the factor active in this phenomenon migrated with the faster moving portion of the gamma globulin

with urticarial allergy to insulin usually contain skin-sensitizing antibodies producing the Prausnitz-Küstner reaction in normal human skin. Lowell (160) showed in 1944 that the sera of certain diabetic patients resistant to insulin contained a factor capable of inactivating heterologous but not human insulin, thus demonstrating the species specificity characteristic of an antibody.

Recent studies have provided further evidence of the presence of substances, apparently antibodies, in the sera of patients treated with injections of insulin which are capable of binding heterologous insulin. Sehon *et al.* (161) studied the serum of an insulin-resistant patient who required 500 units daily by starch zone electrophoresis. They found that the beta and gamma globulin fractions of the serum proteins were increased. The insulin-binding factor was associated mainly with the gamma-2-globulin. Burrows, Peters & Lowell (162, 163) studied the reaction of sera of three insulin-resistant diabetics with bovine insulin labeled with I-131 by paper electrophoresis In all cases the labelled insulin was found to move with the leading edge of the gamma globulin. Insulin mixed with the sera of normal persons or nonresistant diabetics did not move in paper electrophoresis or moved with the albumin The insulin-binding capacity of the sera varied from 0 05 to more than 20 units per ml. Human insulin was not bound by the sera-binding bovine insulin.

While true insulin resistance is rare, the binding of insulin by plasma proteins was shown by Berson *et al.* (164, 165) to occur in essentially all patients who have been treated with it for three months or more. In such patients, insulin I-131 disappears from the plasma more slowly than in patients never treated with insulin or treated for shorter periods The persistence of insulin I-131 was shown to arise from a binding by plasma globulin which satisfies the criteria of an antibody, but does not precipitate with insulin. The globulin-insulin complex moved with the leading edge of the gamma globulin or in the beta-gamma interzone in paper or starch electrophoresis. In the ultracentrifuge insulin was shown to move with the globulin of treated patients, but with the albumin of untreated controls

The insulin-binding activity of the serum was found to be associated chiefly with beta globulin but occasionally with gamma, when serum was fractionated by electrophoresis or by the ethanol method (166) The binding of insulin by antibody inhibited its breakdown by liver insulinase and also its hormone activity (167). The similarity of these findings to those of Burrows, Peters, and Lowell in paper electrophoresis with sera of insulin-resistant patients strongly suggests that the same type of antibody is involved in both resistant and nonresistant patients, but in varying amounts.

Other evidence of anti-insulin antibodies in the sera of diabetics treated with insulin but not resistant to its action was offered by Arguilla & Stavitsky (168). Insulin was coupled to red cells by the *bis*-diazotized-benzidine method and hemagglutination sought with the sera of 23 diabetic patients. Eleven showed hemagglutinating activity Of these, 7 had taken doses of

Miescher & Strassel (181) reported hemagglutination by L.E. sera of tanned sheep cells coated with thymus nucleoprotein and DNA from calf's thymus. Cells coated with RNA from yeast were not agglutinated. The hemagglutination reaction was correlated with the Hargraves' phenomenon in three of four cases.

From these data, it appears that sera of many patients with disseminated lupus erythematosus contain antibodies which will react with nucleoprotein from many different species. This antibody is probably the active factor in the L.E cell phenomenon. In many cases there is also an antibody reaction with DNA. The relationship of this to the L.E. cell phenomenon is less certain. RNA is apparently not involved.

fraction. In the ultracentrifuge it was shown to sediment with the bulk of the gamma globulin at a rate of approximately 7S, thus showing chemical characteristics consistent with those of an antibody. When active sera were incubated with calf, rabbit, or human leucocytes, the activity producing L.E. cells was absorbed. In one serum, this inactivation was accompanied by a reduction of gamma globulin content from 20.5 to 19.8 mg./ml. When the nuclei used in the absorption were washed free of serum and incubated with normal human leucocytes, they were phagocytized to produce L.E. cells. A portion of the adsorbed globulin could be eluted from the nuclei, and was found to be completely precipitated by antigamma globulin serum. Nuclei incubated with L.E. serum were shown to be stained intensely by fluorescent rabbit antihuman gamma globulin serum. When nuclei were treated with deoxyribonuclease to remove deoxyribonucleic acid, they no longer reacted with active sera. Treatment with ribonuclease did not affect the reaction.

Friou *et al.* (177) also demonstrated that nuclei from the mouse, rat, guinea pig, rabbit, man, calf, hen, and carp exposed to active L.E. serum adsorbed gamma globulin which could be stained with fluorescent antihuman gamma globulin rabbit antibody. If the slides were exposed first to nonfluorescent antihuman rabbit serum, subsequent staining with the fluorescent antibody was inhibited. Similar results were obtained when deoxyribonucleo-protein (nucleohistone) from a variety of different animal species was fixed on slides, incubated with L.E. serum, and then stained with antihuman fluorescent antibody (178). Artificial mixtures of DNA and histone also reacted with the L.E. sera. Absorption of active L.E sera with nucleohistone abolished the capacity both to produce this reaction and to induce formation of L.E. cells

The sera of L.E. patients which induce the Hargraves' phenomenon have also been shown to manifest other evidences of antibody activity Robbins *et al.* (179) reported that sera from L.E. patients fixed complement when incubated with nuclei derived from many different species and organs, and with calf thymus nucleoprotein. Most of these sera also fixed complement in the presence of DNA derived from calf thymus, human leucocytes, salmon sperm, and pneumococcus, but certain sera reacting strongly with nuclei did not react with DNA Sera from normals and patients with hyperglobulinemia from other causes did not react Absorption of L.E sera with nuclei removed the L.E factor and reduced or abolished the complement-fixation with nuclei but did not affect the complement-fixation with DNA. Absorption with DNA reduced the complement-fixation with DNA, but did not affect the formation of L.E. cells or complement-fixation with nuclei Some L.E. sera gave precipitin reactions with DNA but the specificity of the reaction was not established. Ceppellini and his associates (180) also noted a precipitin reaction of one L.E serum with DNA This serum also gave complement-fixation with DNA Absorption with DNA inhibited the reaction, while adsorption with RNA did not.

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NEOPLASTIC DISEASES (CANCER)[1,2]

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A pathologist who must report on recent progress and actual trends in cancer research may well confine himself to his own field because the most dramatic achievements during recent years have been realized in experimental research concerning the etiology of neoplastic processes, the morphology, and physiological behavior of cancer cells and tissues.

A high tribute should be paid to the *New York Academy of Science* whose activity covers, in many fields, the whole story of progress so that simple enumeration of some of the most recent symposia reflects the highlights in modern cancer research: Cancer Cytology and Cytochemistry (1956), Homotransplantation (1957); Cellular Biology, Nucleic Acids, and Viruses (1957), Subcellular Particles in the Neoplastic Processes (1957), Virus in Search of Disease (1957), Immunology and Cancer (1957), and Comparative Clinical and Biological Effects of Alkylating Agents (1958). *CANCER*, the monumental work edited by R. W. Raven (6 volumes, Butterworth Publ., London), is now completed. Owing to the high authority of its contributors and to its scope, encompassing as it does the whole field of cancer, it will be a reference work for all those interested in the various domains of cancer research in the years to come.

The May issue of the *British Medical Bulletin* (Vol. 14, No. 2, 1958) brings the main contributions of a symposium in which Alexander Haddow acted as chairman and E Boyland as scientific editor Here are excellent articles concerning chemical and radiation carcinogenesis, as well as recent developments in the field of tumor immunity. The publication of this issue has been very opportunely timed in that it appeared just before the Seventh International Cancer Congress held in London from July 6 to 12, 1958, which, through its excellent planning and the overwhelming number of participants, has been the most remarkable gathering of cancer specialists ever held

Etiology

Virus tumors—Studies carried out in this field have yielded spectacular results which have uprooted even the deeply implanted scepticism of those who until recently considered virus tumors merely as a curiosity and as an utterly unimportant though much advertised group of neoplasms.

Morphological studies of the virus corpuscles (1 to 9) have revealed rather complex structures, totally different from normal cell components such as RNA or Palade granules, so that all speculations based upon the

[1] The survey of the literature pertaining to this review was completed in July, 1958

[2] The following abbreviations will be used ATPase (adenosinetriphosphatase); DNA (deoxyribonucleic acid), RNA (ribonucleic acid).

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whether all sarcoma cells are virus-producing or only a small percentage, as has been claimed repeatedly (30, 31). The cells of myeloblastic leukosis maintained *in vitro* for six months show a steadily increasing output of virus particles at a much higher level than the Rous sarcoma cells (about 1500 particles per cell in 48 hr.) (32, 33).

Attempts at purification of Rous virus are being carried out in various laboratories and are beginning to yield encouraging results (34). Nucleic acid extraction of partially purified Rous sarcoma virus has yielded RNA, the concentration of which parallels the infectivity of the extracts (35, 36); but no preparation of RNA has so far been obtained that is known with certainty to be devoid of virus particles.

Shope's fibroma virus is the only mammalian tumor agent which has been submitted so far to successful studies *in vitro* (37 to 40). Inoculated into monolayer cultures of rabbit testicle cells, the virus undergoes a typical growth cycle beginning with a complete eclipse phase which lasts about 4 hr. After that period, a soluble antigen appears in the culture fluid and its titer increases slowly. No corpuscular antigen is present. The cells contain a viroplasm composed of DNA and RNA. Within this zone, corpuscles are formed from the ninth hour onward and at that time the culture becomes infective. The virus production increases until the fourth day and ends in disintegration of the infected cell. Fresh cells can be infected with this virus and several growth cycles have been observed.

Very interesting results were obtained by the application of fluorescent antibodies in the study of Shope papilloma (41). Antigens could be detected only in the nuclei of the superficial keratinizing cell layers and not in the dividing cells of the deeper layers. This implies that the virus in its effective, growth-promoting form is really masked, in conformity with Shope's ideas and is probably represented by nucleic acids hidden in the genetic structures.

In careful transplantation studies, Greene (42) confirmed some of his earlier findings in showing a distinctly enhanced heterotransplantability of rabbit's skin infected *in vitro* with Shope papilloma virus. This phenomenon became apparent within 3 min. after infection, which means that the virus brings about an immediate change in the biological behavior of the infected cell, increasing its autonomy and acting apparently as an ideal initiating agent.

As far as Bittner's milk factor is concerned, two main facts have emerged in recent years. First, there is the wide diffusion of the tumor agent in wild house mice as found by American and Russian investigators (43, 44). The epidemiologic implications of this fact are highly instructive. They stress the importance of insufficient lifespan and nutritional hardships which are probably responsible for the scarcity of mammary cancers in wild hosts, in spite of the widespread distribution of the agent. The other fact is the presence of subcellular structures identical to those occurring in cells producing the milk factor in apparently virus-free strains of mice (7, 45). This seems to indicate that negative bioassays do not rule out the possibility that

assumption that tumor viruses are merely a special type of cell particles such as microsomes or plasmagenes, are no longer in accordance with the observed facts. Oncogenic agents in birds behave like other exogenic viruses with a definite epidemiology. Exogenous or contact contamination plays a predominant role as has been convincingly demonstrated by many students of avian lymphomatosis (10), but transmission from parents to offspring is also very important as was evidenced by the outstanding experimental work of Burmester and his associates. Since then, the presence of viruslike particles in normal chick embryo tissue culture cells has been repeatedly reported (11 to 14); quite recently the results of very thorough studies utilizing ultrathin sections of normal chick embryos (15, 16) have demonstrated the presence of particles, morphologically identical to those of the leukosis-sarcoma group, in the spleen and bone marrow reticulum cells of about 10 per cent of normal embryos.

Knowledge of this extraordinary diffusion of latent virus infection has contributed a great deal toward dispelling the mystery which has shrouded the epidemiology of fowl leukosis and sarcomas. Two other discoveries were of outstanding importance in this respect: the predominant influence of genetic factors (17, 18) and the extraordinarily wide variation in individual susceptibility which, from one bird to another, may vary 24 millionfold (!) (19). The most significant trend in modern oncogenic virus research is the shift from qualitative to quantitative procedures and problems. Virus titrations carried out initially by the dilution end-point method and later on by the somewhat more refined technique of the 50 per cent lethal dose (LD_{50}) determination, have been replaced by more subtle and less expensive methods such as. (*a*) the incubation period determination first applied by Bryan & Beard (20) in their classical research on Shope papilloma; (*b*) Keogh's procedure (21) in which the microtumor or pock count on the chorioallantoic membrane gives a direct appreciation of the number of virus particles present in the inoculated material (22 to 24); (*c*) the determination of the ATPase titer which, in the blood of myeloblastic chickens, closely parallels the number of virus particles (25), (*d*) the survival time after intracerebral injection in newly hatched chicks (26), (*e*) the adaptation of the Dulbecco-Vogt plate count method (27); and (*f*), last but not least, the direct count of the virus particles in the infected tissues (4, 28).

One of the outstanding results of these quantitative studies was the recognition that the amount of virus extractable from a given tumor is directly related to the amount of virus used to initiate that tumor (29). When very small (less than 1 LD_{50}) doses are used, tumors which yield no recoverable virus at all can be produced and serially propagated This seems to indicate that Rous virus, contrary to most of the other nononcogenic viruses, is in a state of continuous parasitism compatible with the survival of the cell which constantly liberates a small amount of virus particles (22). Because of thermal inactivation of the virus, the titer remains about the same even in cultures with exponential growth: about 1 virus particle for 25 cells. However, many questions remain unsettled. Above all, one may ask

filtrates from four neoplastic processes: two transplantable sarcomas, Ehrlich's carcinoma in ascitic as well as in solid form, and a transplantable myeloid leukemia (Sov. 16). The cell-free extracts were injected into one- to three-day-old mice and four to eight months later leukemias appeared in 45 to 67 per cent of the animals.

Several facts are especially noticeable in this type of leukemia: the increase of virulence obtained through intracerebral passage, the transmissibility to rats by intracerebral inoculation, the enhancement of receptiveness by whole-body irradiation with x-rays, the transmissibility, even to adult animals, on application of carcinogenic hydrocarbons and of cortisone Strain specificity is much less restricted than in the Gross type leukemia; three strains proved sensitive. Noninbred animals were successfully used in these experiments The agent is distinctly antigenic and potent rabbit antiserum was obtained with high protective power.

Schoolman and his colleagues (60) have isolated a new strain of filterable leukemia and lymphosarcomatosis in C3H eb mice which can readily be transferred to adult mice of the same strain in which it induces leukemias within 12 to 20 days in about 70 per cent of the injected animals Brain tissue appeared to be an especially rich source of the etiologic agent, a fact which is in accordance with Graffi's previous findings

Further studies of these mouse leukemias have progressed along various lines of which the following three seem to be the most important. (*a*) Parotid gland tumors produced in C3H mice by inoculation of AK filtrates are notoriously poor in virus and difficult to grow and transplant (61), but when tumor cells or extracts are introduced into cultures of monkey kidney, mouse embryo, or chick chorioallantoic membrane cells, an increase of the tumor-producing capacity occurs within two weeks and a high percentage of mice inoculated with supernatant fluids produce tumors of various types: salivary gland tumors, adrenal tumors, epithelioid thymic tumors, and proliferative lesions of the renal epithelium (62, 63). The culture fluid even proved to be pathogenic for hamsters less than one day old, inducing in a large proportion and within less than 33 days such malignant tumors as parotid tumors, thymomas, sarcomas of the subcutaneous tissue, kidney, breast, gastro-intestinal tract, carcinomatous hemangiomas, etc. (64, 65).

(*b*) The transmission of AK leukemias to C3H mice with RNA prepared from leukemic organs appears to be effective and produces leukemias and parotid tumors (66). There is no reason, however, to draw untimely conclusions from these experiments in considering oncogenic agents as cell products and transmission of tumors by filtrates as subcellular or RNA transplantation. Viruses, in general, are nothing but nucleic acid missiles and the fact that nucleic acid alone can be effective, though much less so than the whole particle, has not the slightest implication upon the nature of viruses.

(*c*) Various experiments suggest that healthy mice may carry latent leukemic or tumor agents which may be triggered by various procedures. Blind transfers of organ extracts between C3H mice may result in 7.5 per cent parotid tumors (67); prolonged administration of cortisone to a breed

virus is present and may be detected by these methods only within a certain threshold.

Indirect evidence for the importance of viral agents in the origin of certain types of cancer in mice has been produced by Reyniers' outstanding experiments with germ-free animals (46). There is a total disappearance of mammary tumors and hepatomas in the C3H strain maintained during several generations in a germ-free environment. The assumption that viruses, when present, act merely as nonspecific growth inciters is clearly dismissed

Leukemias and virus tumors in mice—Since the fundamental discovery of Gross, new types of filterable mouse leukemias have been isolated and are under investigation in various laboratories.

The leukemias studied by Gross (47, 48) are the classical lymphoid leukemias of the mouse which originate in AK mice and which are not only strain—but even subline—specific (49) Quite recently (50), cell-free extracts of C58 mice with lymphatic leukemia have been successfully transmitted to mice less than 12 hr. old of either CBRBr and C3H strains.

The virulence of the AK extracts appeared highly variable from the onset (18 completely negative out of 170 different donors), consequently Gross adopted the method of pooling his extracts before inoculation and later he tried to select virulent strains by inoculating only those extracts from mice which developed leukemia at the earliest date. One of the strains isolated by this technique (strain A) has a considerably increased age range (mice inoculated as late as 14 days of age show 80 per cent, and adults 37 per cent positive results), and a shortened (two to three months) latent period (51, 52).

Friend's leukosis (53, 54) first appeared in 14-month-old Swiss mice which had been inoculated at birth with a cell-free extract of Ehrlich's ascites carcinoma. Extracts of the enlarged spleen gave positive results upon intraperitoneal inoculation into adult Swiss mice and the disease could then be easily transferred by cell suspensions as well as by filtrates of blood and by various organs, with a very high frequency of takes, usually exceeding 85 per cent of the inoculated animals. The disease, a reticulomonocytic leukemia with a tremendous enlargement of spleen, liver, and lymph nodes, appears after a short latent period of only two weeks and lasts for two to three months. The agent, very resistant to lyophilization and cold storage, behaves like a virus, and viruslike particles are present in the involved tissues (55); they closely resemble the particles found in lymphocytic choriomeningitis and Bittner virus but it has been conclusively shown that there is no relationship whatsoever between this leukemia and lymphocytic choriomeningitis (54) Strain specificity is much less pronounced than in Gross's leukemia. Transmissions are positive in Swiss and DBA[2] mice; PRI, C57B 1/6 A, C3H, and F_1 (C58×BA1B) are resistant. It can, however, be transmitted to C3H adults after passage through C3H newborn mice. Vaccinations with formolized virus suspensions protect the animals in as high as 80 per cent of the cases (56).

Graffi's chloroleukemias (57, 58, 59) originated in mice injected with

Another approach to the discovery of viral agents in human tumors is the detection of specific tumor antigens which, of course, are not necessarily viruses but may be autoantigens formed in the course of the carcinogenesis. Zilber (77), with his specific anaphylaxis desensitization technique, was able to reveal specific antigens in numerous human tumors as well as in typical virus tumors, which are adsorbed by red cells and which are not present in normal homologous tissues. Furthermore Grabar & Williams' technique (78) of immune electrophoresis may prove to be very helpful in this respect.

In general, tremendous progress has been achieved in this developing area of virus tumors. Not only have a considerable number of new virus tumors been disclosed, covering the whole field from benign tumors to malignant neoplasms, sarcomas, carcinomas, and leukemias in various species, but a series of facts are now established which undoubtedly favor a more general acceptance of the virus theory of cancer which, of course, remains speculative at the present time. These facts are the wide distribution and extraordinary variety of latent and tumor viruses; precise experimental conditions which permit one to understand why, in a virus tumor, the virus may not be detected by the electron microscopic or bioassay methods, and the viral nature of neoplastic processes promoted by x-rays or hormones.

Criticism, of course, is always possible and even necessary but there is no reason to overdo it. If Law (79), for instance, states that it would indeed be premature on the basis of present evidence to state that mouse leukemia is demonstrably caused by a filterable virus, one may ask if he is aware that similar objections may be raised against the pathogenic role of almost any microorganism One of my old professors and a man of high reputation used to teach us that tuberculosis was a primary disturbance of intracellular fat metabolism and that Koch's bacillus with its waxy membrane was but a by-product carrying, perhaps, the faulty enzyme systems from one cell to another. These discussions may be interesting, but here are leukemias and mammary cancers which are highly lethal and experimental evidence points out that vaccines and antisera prepared with the respective viruses can prevent them. It is, perhaps, more urgent therefore to focus the attention on these virus particles rather than upon their ultimate and intrinsic significance.

Perhaps nothing better demonstrates the unpredictable tricks which nature has in store for those who endeavour to assemble the strangely shaped pieces of the puzzle called carcinogenesis than the pertinent observations on metals, plastics, polymers, and surfaces

"Metallkrebs," cancer due to the influence of metals, was the idea which emerged from a long-term experimental study undertaken by Schinz (80, 81) to see whether chromium, cobalt, and arsenic implanted into the femur of rabbits could promote neoplasms. They did—not only bone sarcomas but pulmonary sarcomas and carcinomas as well Since then the carcinogenic activity of metals and their salts has been thoroughly investigated by many authors It has been confirmed for chromium (82a), arsenic (82b), and cobalt (83). Similar demonstrations have been made with respect to mercury (84), nickel (85), and lead salts (86) Beryllium has aroused special interest be-

f mice (C58×AKR) with a high incidence of leukemia was followed by he development of parotid tumors; the same results were obtained with a C3Hf strain of Gross but not with a C3Hf Hu derived from an Andervont subline (49); total body irradiation of C3H and C57 BR mice produced thymic lymphosarcomas and leukemias which, upon cell-free transfer to newborn mice of the same breed, produced 8 per cent leukemia and 5 per cent parotid tumors (68, 69) All these experiments suggest that in this whole group of mouse leukemias and tumors, not one but a great number of viruses are involved. These have been stirred from their latent state by experimental procedures which happened to produce ideal conditions for the display of their activity, and it remains for future investigations to determine the relationship that may exist between these different agents. In spite of numerous investigations being conducted in many laboratories no clear cut case of virus detection in human neoplasms has so far been reported.

Some significant clues favoring a possible relationship between hepatoma and virus hepatitis have been brought forth (70) and, in relation to lung cancer, a special inflammatory condition of the bronchial epithelium for which Papanicolaou has coined the name, "ciliocytophthoria" (destruction of ciliated cells), may be of special interest (71, 72). This is a mass destruction of ciliated epithelium associated with an acute respiratory disease of established or presumed viral origin (73). The smears contain numerous tufts with pinched-off distal portions of the cells. The nucleated basal fragments of the cells show a characteristic pattern of nuclear degeneration and very frequent acidophilic inclusions which, in Papanicolaou's opinion, resemble those described in various cell types as resulting from virus activity. This bronchial disease appears to be related to lung cancer which was present in 12 per cent of the cases so far detected.

Viruslike particles have been observed in electron microscopic examinations of lymph nodes in human patients afflicted with leukemic conditions (7, 74). These pictures are very interesting but, of course, it must still be shown that these are the agents of the disease and not merely innocent saprophytes. The discovery of latent viruses on a widespread scale which the present writer predicted many years ago (75) has meanwhile come true and an entire symposium was recently devoted to these "viruses in search of disease" or "orphan viruses," as they have been expressively called by Duran Reynals (76).

It will always be difficult to establish a causal relationship between virus particles and the etiology of the tumor in which they are found, especially when human material is involved, but the recent developments of tissue culture techniques and heterotransplantation open up new avenues for a direct experimental study of human cancers. Stewart's findings (61 to 65) especially have disclosed very promising procedures in this field An ideal method appears to consist in infecting tissue cultures of various types (human tumor cells, monkey kidney cells, mouse embryos) with tumor extracts, maintaining these cultures for at least 14 days and inoculating the supernatant fluid into newborn hamsters. This animal, because of its special genetic background, seems ideally suited to such experiments.

ing results with the tagged polymers (94). Plastics, which seemed to be inert substances which would remain unaltered in the body during an entire lifetime, proved to be less stable than expected. At some point between 22 to 26 weeks after implantation, rats began to excrete radioactive material in the urine and urinary radioactivity disappeared when the plastic was removed. It was not possible to link this radioactivity to a specific degradation product but the breaking down of the polymers was demonstrated and it appeared logical then to attribute the carcinogenic activity of the polymers to some free radical known to effect depolymerization of nucleic acid. It could also be assumed that the creation of reactive centers at the surface of the degrading polymer could lead to the fixation of some proteins and impair the metabolism of the adjacent cells. Obviously, the tendency had shifted toward some specific chemical interference

Then, again, evidence turned to the other side, mainly through the demonstration of carcinogenic effects obtained with all kinds of substances such as rubber, platinum, horn, ivory, silk film, and glass provided they offer a smooth, uniform surface of at least 5mm in diameter (95 to 98b). Buttonlike discs 18mm in diameter with a thickened margin seemed to be most suited for producing sarcomas When implanted in the form of powder the same substance proved innocuous. So it seemed that the mechanical condition was of paramount importance in the formation of the foreign body sarcomas, related, perhaps, to a certain tension of the collagen capsule with secondary circulatory disturbances, leading to inhibition of cellular respiration in the sense of Warburg's theory.

New light was shed on the problem by the unexpected results of experiments with the macromolecular polyvinyl pyrrolidon (99) which, during World War II, had been widely used as a substitute for plasma. When implanted in powdered form into the subcutaneous tissue, or injected intravenously as a solution into mice and rats, this substance appeared highly carcinogenic and induced malignant tumors in as many as 32 per cent of the animals in some series. The tumors appeared not only at the sites of injection but in the internal organs in three waves—the first mainly composed of reticulum cell sarcomas, with a peak at 13 to 15 months, the second as Kupffer-cell sarcomas in the liver, and the third as carcinomas affecting uterus, skin, ovaries, and breast The main point is that these substances stay in the body where they are engulfed by macrophages. According to Hueper, they may act by interfering with intracellular polymerization or by forming abnormal conjugation products with proteins or nucleoproteins through cross linkage Here, then, is another example of absolutely inert and innocent looking compounds proving to be highly dangerous because of their definitive inclusion within the cells where they create metabolic disturbances resulting in carcinomas The fact offers a severe warning never to use substances which stay permanently within the organism!

It becomes evident that we must consider various types of cancers: (*a*) true metal cancers caused by chromium, arsenic, cobalt, lead, mercury, nickel, beryllium, and possibly selenium, (*b*) silicate cancers obtained with

cause of the severe pulmonary injuries caused by this metal and its compounds and the slow-healing wounds which result from the contact of this substance with the skin (83, 87).

There is no doubt, then, that several metals and their compounds are directly carcinogenic. This action is probably very complex in nature, resulting perhaps from enzyme inhibition (alkaline phosphatase in the case of beryllium), to the formation of chelates, protein compounds by combination of the metal with amino or sulfur radicals. Beryllium acts directly on nucleic acid causing depolymerization and mitotic disturbances somewhat similar to colchicin.

Further studies (88) carried out with silver, stainless steel, tantalum, tin, and vitallium (an alloy of chromium, cobalt, and molybdenum) aroused considerable interest because they concerned metals which are widely used in surgical and dental repair work. With the exception of tin, all of them caused sarcomas when implanted as metal foils into the subcutaneous tissue of rats. However, the data became conflicting in so far as they interfered with a quite new principle of carcinogenesis, the action of foreign bodies with smooth surfaces of a certain dimension. Tin foils, because of their consistency, did not retain their form but crumbled and significantly caused no sarcomas. The other metals remained intact but proved not to be carcinogenic when applied in the form of powder or salts.

The action of smooth surfaces was discovered by chance, which remains the great master in experimental pathology. Turner (89) was the first who, by implanting discs of bakelite into the subcutaneous tissue of rats, obtained sarcomas and his results, published in 1941, would have passed unnoticed had not the development of sarcomas been observed later by Oppenheimer, Oppenheimer & Stout (90) in rat kidneys wrapped in cellophane to produce hypertension.

The next contribution came from Zollinger (91) who had observed sarcomas in rat kidneys compressed by Acril-Resin (Du Pont Company) capsules. He advanced two steps toward an explanation of these tumors. Pointing out that the sarcomas arose in close contact with the plastic at the inside of the capsule in the compressed and probably ischemic area, he incriminated not the chemical action of the substance but the mechanical disturbance it created. He inserted the same plastic in the form of small rods with a roughened surface into the subcutaneous tissue of rats and mammary glands of C3H mice with no effect, which gave some hint that the texture of the surface might be of importance. In further experiments (92, 93), all kinds of plastics, polyethylene, polyvinyl, teflon, nylon, 'orlon, and dacron were found to induce sarcomas after one to two years when introduced as films, foils, or platelets. Sometimes, the percentage was as high as 45.4 per cent, but the materials proved totally ineffective when implanted in the form of fibers or powder. At this time, too, it could be shown that perforated membranes produced fewer sarcomas than intact ones and one sarcoma appeared 659 days after the implantation of a glass cover-slip. The question of surface seemed to be of paramount importance. And then came the surpris-

ated in small quantities as a byproduct of purine metabolism and excreted in the urine is also carcinogenic (111).

Cytology and Pathology

Sex chromatin.—Well known since its discovery by Barr & Bertram (115), this substance is often present in nuclei of cancer cells. In females, the tumors are always of the carrier's sex and this holds true even for arrhenoblastomas, i.e., for virilizing tumors formed by Berger's cells which, on the basis of the evidence available, correspond to the Leydig cells in males. This demonstrates complete independence between cellular sex and secretory activity (116). In male genital glands, however, female tumors may be found, which is logical since the male germinal cells possess the elements of both sexes. It is therefore not surprising that in males not only testicular teratoma but even a mediastinal teratoma of the female sex (117) has been observed. This may be an argument in favor of a parthenogenetic as opposed to a blastomeric origin of these tumors

Since the early observations of Gey (118), Earle (119), and Earle & Nettleship (120), malignant transformation of normal human and animal cells during a prolonged period of culture *in vitro* has repeatedly been observed (121 to 126), and is, at present, one of the most fascinating problems of experimental cytology. A recent report giving interesting cytobiological data is given by Moore (127). Normal cells maintained in culture may, after some time, display changes both with respect to their morphological character (especially chromosome number) and metabolic behavior, without being necessarily malignant in nature Biological control through implantation in homologous or heterologous hosts is, of course, always necessary to establish malignancy in demonstrating uncontrolled growth, invasiveness, and metastatic spread of the changed cells (128) This opinion is scientifically sound and indisputable but from the practical standpoint the problem looks somewhat different and becomes really embarrassing when the decision has to be made whether malignant looking human epidermal cells grown *in vitro* should be used for grafts although their biological malignity is not warranted by reliable tests.

The causes of these neoplastic transformations are unknown. It is possible that the prolonged maintenance of cells in heterologous culture media and in the more or less hypoxic state which always prevails in tissue cultures (129) is, in itself, detrimental and promotes a continuous process of selection by which cell types less suited to the environment are progressively eliminated. Swim & Parker (130) believe that permanently proliferating cells are already specially adapted nutritional variants The genetic instability of these cell lines manifests itself by chromosomal changes which may lead through a series of transitional steps to malignancy

According to this theory, the conditions realized in cell cultures would be in themselves carcinogenic. But there are other possibilities. One might presume that potentially malignant cells are already present in the normal tissues which are explanted (131). On the other hand, one must not forget

asbestos (filamentous or ribbonlike polymer of silicate) (100, 101, 102), and also with quartz (sand power) (103); (c) polymer cancers; and finally (d) the surface cancers which are dependent *upon the physical form* of the substance introduced.

The conclusions applied to human pathology may not be as alarming as they might appear to be at first sight. It is possible that the carcinogenic factors outlined in this chapter pertain only to some species, especially rodents, which seem to be particularly predisposed. In other species, for instance, chickens (personal unpublished data), such substances have not so far yielded tumors. The surface factor does not seem to be of importance in humans. Indeed, a tremendous number of foreign bodies, especially projectiles, shell splinters, orthopedic prostheses of all kinds, have been well tolerated for many years and not a single observation of sarcoma arising at the site of those foreign bodies has come to our knowledge. The same holds true so far for polymers used as plasma ersatz, but it would be wise not to disregard entirely the possible implications of these experiments and to avoid as far as possible, the introduction of all such foreign bodies into the human organism.

The space devoted to the preceding topics does not allow us to examine the details concerning the all important area of chemical carcinogenesis. An inspired account of the last eleven years' achievements in this domain is given in the above-mentioned special issue of the *British Medical Bulletin*. Interest remains focused on the intracellular pathways of clinical carcinogenesis. Alkylating carcinogens probably operate directly upon the deoxyribonucleic acid of the chromosomal structures, explaining in this way their behavior as radiomimetic agents (104). Carcinogenic hydrocarbons and azo-carcinogens may act by binding with key proteins, nucleoproteins, or enzyme proteins (105, 106, 107), essential for the regulation of growth, a concept which has found its expression in the "deletion hypothesis" of cancer. This, in turn, may lead to quantitative or qualitative changes in the nucleic acid synthesis which would in the end be responsible for the neoplastic transformation, so that initially different routes may lead to similar end results.

The much discussed (108) carcinogenic activity of cholesterol in mice has been reaffirmed (109). Roffo's (110) repeatedly criticized contention concerning the carcinogenic action of oxidation products of cholesterin has become plausible through recent investigations which have led to the discovery of several hitherto unknown compounds (111).

The search for carcinogenic compounds among the substances normally liberated and excreted by the organism as by-products of the intermediary metabolism has led to the discovery of two interesting groups of substances. 3 hydroxykynurenine and 3 hydroxyanthranilic acid which are intermediary products of tryptophan metabolism and are usually excreted in minute quantities in the urine. These substances have been tested by the bladder implantation procedure of Bonser and found carcinogenic in mice (112). Hydroxyanthranilic acid is excreted in increased quantities by patients afflicted with bladder cancer (113, 114). Another substance, xanthin, liber-

convincingly shown that the administration of bone marrow or spleen to mice exposed to high x-ray doses allows the recovery of the animal by proliferating in the new host. But it came as a surprise that this foreign tissue could be definitely established in the new host and give rise to a mosaic of erythrocytes (radiation chimeras) (152, 153, 154). The range of tolerance concerning the medullary tissue injected seems to be variable. In mice, isologous marrow produces lasting recovery. Bone marrow of rats may keep irradiated mice alive (155), and the rat leukocytes appear in the peripheral blood where they are easily detected by the positive reaction to alkaline phosphatase. But there is no record of prolonged survival in these cases and, in general, even homologous marrow after securing temporary recovery leads to so-called "second phase of irradiation syndrome," or "secondary disease" (156), which is attributed to an immune response of the grafted marrow against the irradiated host (157). This has been conclusively proven by the use of co-isogenic lines differing at the histocompatibility locus H_2 (158). The logical step to preclude the unwelcome reaction is the use of embryonal bone marrow which (159) has been quite successful. Rats seem to be more receptive to homograft of bone marrow and homografts definitely established supplying as high as 95 per cent of the recipient's red blood cells have been observed (160). In these cases of established chimerism, the definite coexistence of two antigenically different types of cells in the same organism can be explained only on the assumption that the cells become "nonreacting," i e , acquire a new immunological state of symbiotism or radiation-induced tolerance (162) Animals carrying foreign medullary tissue can be successfully grafted with skin of the same genetic constitution as the donor of the bone marrow (161). The same holds true for tumor grafts which provide an excellent material for the study of the complicated immune responses in these radiation chimeras (162). The application of this principle may be manifold and very important Lethal effects of bone marrow destruction by antineoplastic drugs such as busulfan (Myleran) and a dimethyl homologue could be overcome by intravenous or intraperitoneal injections of isologous bone marrow (163, 164) The procedure along which further research could be carried on to secure heterograft could be to inactivate the immune response to an extent that would allow transfusion of medullary cells, once this transplantation is established the animal should be tolerant to the transplant of the donor tissue (160).

A pathologist may be excused if he finishes a report on the progress in cancer research without treating at length the question of therapy. Perhaps his ignorance is not altogether to blame for this but also his conviction that no essentially new discoveries have been achieved since the publication of last year's article (C. G Zubrod, *Annual Review of Medicine*, 1958) Hormonotherapy has made slow but steady progress and in this domain Bauer's (165, 166) procedure of pituitary destruction through the introduction of radioactive material by transethmoidal puncture deserves special mention. Chemotherapeutic research is carried on with ever increased fervor Two symposia held under the auspices of the International Union in Rome and in

that cultivation *in vitro* provides ideal conditions for the activation of latent viruses which could have been present in the explanted cells. At any rate, the comparative study of cells from "germ-free" animals or from animals with very different spontaneous tumor rates such as mice and guinea pigs in prolonged tissue cultures could possibly furnish some interesting clues in this respect.

The invasive properties of cancer cells have been studied with new tissue culture techniques (132, 133). The particular behavior of the cell surface is certainly of considerable importance, especially in the first stage of invasion. Changes in adhesiveness and ultrastructural behavior of the cell membrane (134, 135), and changes in electric charge accompany the suppression of contact inhibition (136) which appears to be a potent factor in promoting autonomy and invasiveness of the cancer cell. Metastasis formation has been reviewed by Zeidman (137). The distribution pattern of metastases depends to a certain degree upon mechanical and hormonal influences but the overall importance of the individuality of each tumor has been clearly demonstrated in recent studies (138) carried on with cell suspensions from ascites tumors. It appears further that normal tissues have a peculiar tumor cell-destroying property which is particularly active in lung tissue (139).

Transplantation.—Considerable progress has been achieved in this field and most of the methods devised to improve results of tumor grafting have been aimed at overcoming the resistance of the host This has been successfully tried in various ways (140) so that heterotransplantation has become a current procedure in modern cancer research. X-rays and cortisone have been the most important tools applied so far in this domain Greene's techniques (141, 142) of tumor implantation into the anterior chamber of the guinea pig eye which yield discouragingly low percentages of takes can be noticeably improved by the administration of cortisone (143), and quite a number of human tumors such as chondrosarcomas, epidermoid- and adenocarcinomas, melanomas, and embryonal tumors, are now currently transplanted and adapted to permanent growth in cortisone-treated hamsters (144, 145). Human pleural or peritoneal cancer exudates have been repeatedly implanted and successfully maintained in the peritoneal cavity of cortisone-treated mice as ascites tumors through numerous passages (146). By combining x-rays and cortisone it has become possible to graft even normal tissues in foreign heterologous species and this technique has opened new ways for the study of general problems related to growth and differentiation (147).

The considerable interest devoted to this field is highly justified because of its immediate practical implication concerning the possibilities of grafting normal tissues such as skin, kidney, or endocrine glands In addition, the heterograft of human tumors to animals provides welcome opportunities for the experimental study of their growth pattern, immunological behavior, sensitivity to x-rays, and for pharmaceutical screening (148).

The effect of x-rays in securing tolerance can be considerably enhanced by bone marrow transplantation. A series of experiments (149, 150, 151) had

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Tokyo have produced an authoritative account of its present status (167, 168). In spite of the tremendous number of substances tested the practical results, as far as treatment of human cancers is concerned, remain highly disappointing. For this reason, efforts are being made to find new ways either by combining different types of treatment (169, 170), or by attempting to put new life into old and obsolete projects such as immunotherapy. We hope that the tremendous effort involved in this struggle will not be in vain in order that future contributors can leave this subject in a less pessimistic mood than the present writer.

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NEOPLASTIC DISEASES (TUMOR CHEMOTHERAPY)[1]

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Introduction

Chemotherapy for malignant disease, being a recent multidisciplinary research projection, is at present undergoing the necessary study upon which the principles for its successful development can be formulated This study was given impetus by war-time research on the physiologic effects of the war gases, sulphur and nitrogen mustard. Scientists with a clinical background were soon investigating the possibility of utilizing the latter substance in the treatment of patients with leukemia and the malignant lymphoid diseases (1, 2). Reports of these early trials were encouraging, and during the intervening years studies of therapeutic drugs for cancer have rapidly expanded and a massive amount of literature has accumulated. A number of current discussions will provide the clinician with a general introduction to the subject.

Haddow, in a previous *Annual Review of Medicine*, examined some of the basic aspects and clinical applications of chemotherapy for neoplastic disease (3) During the period covered by this review, the proceedings of the Third National Cancer Conference (4), of the Henry Ford Hospital Symposium on the Leukemias (5), and of the Sixth International Congress of Hematology (6) were published. The papers presented at the Conference on Comparative and Biological Effects of Alkylating Agents (New York Academy of Sciences and the Cancer Chemotherapy National Service Center) were published in one monograph (7), comparable in scope to the previous compilation of papers dealing with 6-mercaptopurine (8).

A comprehensive bibliography on chemotherapy for cancer covering the years 1946 to 1954, inclusive, was prepared through the cooperative efforts of the Armed Forces Medical Library, the Committee on Chemotherapy of the National Advisory Cancer Council, and the National Cancer Institute (9). After scanning the world literature for 1951 through 1955, Hirschberg selected from review articles on cancer research those which appeared most useful for reference (10). One part of this list included reviews specifically concerned with various forms of treatment and clinical studies

Standard textbooks of pharmacology and therapeutics included chapters on cancer chemotherapy (11 to 14), two of which were contributed by Karnofsky (11, 12). Sampey assembled bibliographies on the clinical uses of 6-mercaptopurine for cancer (15), anticancer agents (16), folic acid antagonists for lymphocytic leukemia (17), and drugs for granulocytic leukemia (18). In

[1] The survey of the literature pertaining to this review was completed in July, 1958

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of the enzyme reactions at various levels in the synthesis of nucleic acids. Patients with leukemia have been treated effectively with the folic acid antagonists, sodium 4-amino-pteroylglutamate (Aminopterin Sodium), and amethopterin (Methotrexate) and the purine angatonist, 6-mercaptopurine. Other folic acid antagonists (adenopterin) and purine antagonists (6-chloropurine, 6-thioguanine, and 8-azaguanine), as well as other types of antimetabolites, have been employed to a lesser extent. Limited experiences with azauracil and the fluorinated pyrimidine, 5-fluorouracil, are being reported.

Several antibiotics obtained from the Streptomyces, including azaserine, diazo-oxo-L-norleucine (DON), actinomycin-C, actinomycin-D, and mitomycin, have exhibited a cytotoxic effect. It has been suggested that the inhibitory action of these compounds might be based upon their antimetabolite activity. Azaserine, for example, has been found to be an L-glutamine antagonist.

Urethan and the colchicine derivative, demecolcin, are general cell poisons which exert an antimitotic influence. Their unique properties have been exploited for cancer chemotherapy.

Some of the compounds mentioned above are tabulated in the final section of this review Their chemical structures are indicated, and references to selected and current literature are given.

The effectiveness of treatment with anticancer agents is necessarily expressed in relative values Scott, in his concise survey of the status of chemotherapy for malignant disease, states that no patient to whom conventional methods can be expected to offer either cure or palliation can justifiably be treated with drugs (23) Chemotherapy has brought about no cures of patients with cancer. The maximum beneficial effect derived thus far has consisted of clinical remissions of modest duration in patients with lymphoid tumors, including the leukemias With few exceptions, those with solid tumors have responded poorly Nevertheless, the results of the use of chemotherapeutic agents are sufficiently encouraging thus far to warrant continued clinical trials of carefully selected drugs in an effort to control malignant disease.

TUMOR CHEMOTHERAPY

Acute leukemias —In the care of children with acute leukemia, therapeutic efforts have been directed chiefly toward eradication of the leukemic process from the hematopoietic system and correction of the pathophysiologic effects of its infiltration of organs and body tissues (35 to 38). Farber (30), Burchenal (35, 37), Pierce (36), and others (39) have recommended the sequential administration of a folic acid antagonist such as methotrexate, and a purine antagonist such as 6-mercaptopurine, and the judicious complementary use of ACTH or other adrenocortical steroids The clinical and hematologic features whereby one could determine the antimetabolite most suitable for initiation of this regimen have not been specifically defined

Folic acid antagonists and purine antagonists each have induced complete

a number of other articles the general subject of drug therapy for cancer was reviewed (19 to 24) and specific groups of agents, such as nitrogen mustard and allied compounds (25, 26), folic acid antagonists (27), and antipurine compounds (27, 28) were discussed. These publications, as well as the earlier reports of Burchenal (29) and Farber *et al.* (30), are valuable sources of information on clinical chemotherapy for cancer.

In view of the vast numbers of papers on basic research in this field, the reader is referred to the volumes in which the present status of chemical compounds and their related bibliographies are given (9, 31, 32). Also, the symposia on Approaches to Tumor Chemotherapy, and Antimetabolites and Cancer, published by the American Association for the Advancement of Science in 1947 (33) and in 1955 (34), provide information concerning investigative efforts to coordinate and develop this method of treatment into a precise scientific discipline Burchenal (29), Farber *et al.* (30), Scott (23), Davis (22), and others (7, 27) have discussed quite comprehensively for the clinician the pharmacologic, toxicologic, and biologic properties of the chemotherapeutic agents. These compounds have been conventionally classified as alkylating agents, antimetabolites, cell poisons, and hormones. Since hormones are not chemotherapeutic drugs in the exact sense, in the present review their usage in only a few types of malignant disease will be mentioned.

The alkylating agents employed clinically include the nitrogen mustards, ethyleneimines, and methanesulfonyloxyalkanes. The prototype of the nitrogen mustards is methyl-*bis*-(β-chloroethyl) amine hydrochloride, commonly designated as mechlorethamine or HN2. Presumably, the 2-chloroethyl radicals are the reactive groups which alkylate by combining with biologically important groups of nucleoprotein in cells. By introducing substituents for the N-methyl group in HN2, other analogues have been prepared in efforts to obtain compounds having more specificity for tumors and less toxic effects upon patients. Among the later nitrogen mustards are the β-naphthyl compounds, designated R-48; the phenylbutryic acid mustard known as CB-1348 or chlorambucil; a 2-chloropropyl compound, novoembichin; a pyridoxine derivative, dopan, and a phenylalanine substituted mustard, sarcolysin. Nitromin, the N-oxide of HN2, and hemisulfur mustard, a derivative of mustard gas itself, particularly the former, have been administered clinically.

Ethyleneimines possess chemical structures related to the reactive cyclic ethyleneimonium intermediates, which are formed by the chemical transformation of nitrogen mustards in neutral or alkaline solution. Three of these compounds, triethylene melamine (TEM), triethylene phosphoramide (TEPA), and triethylene thiophosphoramide (Thio-TEPA) have been employed extensively in the treatment of patients with cancer. The methanesulfonyloxyalkanes are also capable of alkylation Busulfan (1,4-dimethanesulfonyloxybutane) (Myleran), dimethylbusulfan (dimethylmyleran), and a nonane analogue of busulfan have been subjected to clinical study.

The use of antimetabolites is directed toward the competitive blockage

that of 209 who were treated with all three types of drugs, 50 per cent survived over 11 months, and 10 per cent survived over 20 months (40). Pierce reported that 35 per cent of 54 treated with the three antileukemic agents lived beyond 12 months (36). The median survival time of 253 children similarly treated by Burchenal and his colleagues was 12.4 months (51). These figures represent significant improvement over the clinical results (a four months' survival of 50 per cent of patients, and 11 months' survival of 10 per cent) obtained before the current therapeutic agents became available (40, 47).

In contrast to the effectiveness of chemotherapeutic agents against acute leukemia in children, in adults the disease has failed persistently to respond to these drugs (52, 53). Through the use of 6-mercaptopurine and its analogues, 6-chloropurine and thioguanine, brief but complete remissions were obtained in only 10 to 15 per cent, and partial remissions in another 20 per cent of adults (53). Cross resistance among the purine antagonists was demonstrated (52). Hepatocellular jaundice developed in approximately one-fourth of 25 patients who were given 6-chloropurine (52). Amethopterin, alkylating agents, and urethan were of little value (52).

Although treatment with adrenal steroids has been considered definitely less successful in adults than in children, practically no response being obtained in patients over 30 years of age (52), Wilson and his co-workers believed the steriods to be the most effective therapy for acute leukemia in adults (53). Recently, the use of massive doses of 9-α-fluorohydrocortisone, prednisone, and prednisolone has been discussed in several papers (40, 42, 54). Ranney & Gellhorn were able to induce complete remissions in five and partial remissions in six of 18 adults by the administration of prednisone and prednisolone in daily doses as high as 1000 mg (43). Based upon a study of 20 adults with acute leukemia, some of whom were given 250 mg. of prednisone daily for two weeks, and the remainder 1000 mg. daily for the same period, Granville *et al.* concluded that therapy with steroids in such massive doses appeared at least as effective as 6-mercaptopurine (55).

Chronic leukemia.—Despite the increasing trend toward the treatment of patients with chronic leukemia by means of chemical compounds, as Bethell points out, it has not been conclusively demonstrated that the subsequent survival time has exceeded, or even equaled, that achieved with roentgen ray or radiophosphorus therapy (56). It is believed, however, that the disease can be controlled with drugs sufficiently to justify their use rather than ionizing radiation (56).

Although the natural history of chronic granulocytic leukemia has been described as "stereotyped and constant" (57), institution of treatment has been recommended as soon as the diagnosis is made (56, 58). Urethan (ethyl carbamate) was employed for a time, with considerable success (30, 56, 59). Recently, the therapeutic effectiveness of a number of polyfunctional alkylating agents has been established (37, 57). Nitrogen mustard (59, 60), TEM (56, 59, 61, 62), Thio-TEPA (63), nitromin (64), BCM (65), E-39 (66), and

remissions of acute leukemia in approximately 35 per cent of patients, exhibited by temporary subsidence of blood and bone marrow abnormalities and clinical manifestations. An additional 25 per cent obtained partial remission, consisting of considerable improvement, though some evidence of the disease persisted (40). In Farber's experience, remissions usually began after about three weeks of treatment with antifolic drugs and after about six weeks with antipurine drugs. Remissions were maintained, on the average, for eight months with antifolic compounds and for less than six months with the antipurines (30). No cross resistance between the two types was observed (37).

Although adrenocortical steroids have produced remissions in a high percentage of children with acute leukemia, they have proved most useful in emergency situations, particularly in the presence of a pronounced hemorrhagic tendency (30, 36, 40, 41). Steroids have been combined with an antimetabolite in efforts to stabilize rapidly the general condition of an acutely ill patient for a period sufficiently long to permit the antimetabolite to exert its full effect (30, 35, 36) Hill and his co-workers have administered massive doses of adrenocortical steroids (hydrocortisone, prednisone, prednisolone, or 9-fluoro-hydrocortisone) in order to induce a quick response or to obtain an additional remission during the terminal stages of the disease (40, 42). Caution against the dangerous side effects of large doses of steroids was voiced (40, 43).

Hyman, Brubaker & Sturgeon observed that the daily administration of large doses (up to 6.6 mg. per kilogram of body weight) of 6-mercaptopurine to children with acute leukemia seemed to induce a somewhat more rapid response than the standard dose of 2 5 mg. per kilogram. The use of large doses for a short period during the initial phase of therapy was therefore suggested. With such a dose regimen, the need for bone marrow examinations at frequent intervals to detect damage to the hemopoietic tissues was stressed (44). Two other purine antagonists, 6-chloropurine and thioguanine, were effective against acute leukemia in children, though they exhibited cross-resistance to 6-mercaptopurine (30, 37)

Following the intrathecal administration of amethopterin (Methotrexate) in doses of 0.1 to 0.5 mg. per kilogram of weight, symptoms incident to infiltration of leukemic cells into the brain and brain covering were relieved repeatedly (45, 46). Whiteside *et al* were able to produce remissions of the neurologic manifestations, beginning about one week after instillation and continuing about six weeks (46) Previously, the development of neurologic signs and symptoms in children whose acute leukemia was otherwise being maintained in a prolonged remission had indicated that antileukemic agents given in conventional fashion did not concentrate in the spinal fluid sufficiently for a therapeutic effect (46)

Despite the difficulties of statistical analysis of survival data (47, 48, 49), extensive clinical experience suggests that the lives of children with acute leukemia were prolonged by chemotherapy (36, 40, 50, 51). Farber calculated

agents for malignant lymphoma (78): (*a*) *Clinical Class II* disease (regional disease with or without constitutional signs and symptoms), and Class III disease (generalized, with constitutional signs and symptoms). (*b*) Emergency situations, such as vena caval syndrome, spinal cord compression, and CNS involvement with increased intracranial pressure. (*c*) Acute toxic syndrome (*d*) Homme-rouge type of mycosis fungoides (*e*) Airway obstruction. (*f*) Widespread skin involvement.

Jacobson also reviewed the present attitudes toward drug therapy for malignant lymphoma (79). Since a flare-up in a single small focus frequently produced systemic disturbances of only short duration, he suggested that patients with recurrences of lymphosarcoma and Hodgkin's disease be treated only when persistent and severe symptoms indicated acceleration of the neoplastic process.

Alkylating agents have been particularly effective in the alleviation of constitutional signs and symptoms of malignant lymphoma (37). Reticulum cell sarcoma responded to CB-1348 (67), nitromin (64), BCM (65), sarcolysin (80), and Thio-TEPA (81). Patients with lymphosarcoma obtained beneficial results from treatment with CB-1348 (67, 76, 79, 82, 83), nitrogen mustard (60, 79), R-48 (77), TEM (79), BCM (65), Thio-TEPA (76) and E-39 (66). Remissions in patients with giant follicular lymphoma were produced also by CB-1348 (67) The majority of those with malignant lymphoma were not benefited by busulfan, though a temporary objective improvement was induced in some and complete remissions in a few (84).

With respect to Hodgkin's disease, the pronounced suppressive action of nitrogen mustard on many of its stages has been well demonstrated (60). TEM has also proved beneficial (62, 79). The effects of Thio-TEPA have been variable (76, 81, 85) Moderately good results were produced by CB-1348 in some clinics (40, 79, 82, 83, 86) and only fair results in others (67, 76, 87). A palliative influence was also displayed by BCM (65) and R-48 (86), though sarcolysin and its isomers were of only slight benefit (88, 89). Of 61 patients with Hodgkin's disease to whom Perevodtchikova gave dopan, 41 were improved (89). Aquirre & Sosa reported that 12 of 15 children received symptomatic relief following treatment with actinomycin-D (90). From an analysis of data on patients with Hodgkin's disease, however, Osgood concluded that survival has not been appreciably prolonged since the introduction of antibiotics and alkylating agents (91)

Adrenocortical steroidal hormones were useful in the control of acquired hemolytic anemia in patients with lymphoma (37). In addition, these steroids exhibited an antitumor effect upon lymphosarcoma and reticulum cell sarcoma, though not upon Hodgkin's disease (37) Moderate to severe adverse constitutional signs and symptoms appeared in five of 11 patients with advanced lymphoma during or immediately after the administration of small doses of methyltestosterone (92).

Multiple myeloma.—Chemotherapy for multiple myeloma has been described by Rundles and his associates (93, 94) This disease has been un-

CB-1348 (67, 68) have exhibited palliative activity. At present, busulfan appears to be the choice of many clinicians (37, 40, 56, 57, 61, 69 to 72). Galton reported a favorable response to this drug in all except one of 42 patients (72). The mean survival time of those who were treated by busulfan was 35.5 months, as compared to 28.8 months of a group who received roentgen irradiation (72). Bethell obtained good to excellent therapeutic responses in 26 of 31 patients, 10 of whom had been treated previously (56).

In a high percentage of patients in the early stages of chronic granulocytic leukemia remissions were produced with 6-mercaptopurine, as well as with 6-chloropurine and thioguanine (37, 59). Since antipurine agents occasionally are effective even during the terminal stage, Burchenal suggested that the administration of other types of drugs during the early phases may be advantageous (37).

The beneficial effects of a mitotic inhibitor, demecolcine (Colcemid), upon patients with chronic granulocytic leukemia was described by Moeschlin (40). A favorable response to this compound has also been reported by others (56, 57, 73) Some observers considered the proliferative and poorly differentiated phase in the terminal stage of the disease the major indication for the use of demecolcine (40, 56). Side effects were produced (57), though the drug did not significantly depress the platelets and erythrocytes—a factor of potential importance in the presence of thrombocytopenia (74).

The wide variability in both the clinical evolution of chronic lymphocytic leukemia and the response of patients to treatment necessitates judicious individualization of drug therapy regimens. Since the disease may run a prolonged benign course, therapy is generally based upon definite indications (37, 56)

Essentially, only the alkylating agents and steroids have been of therapeutic value in the care of patients with symptomatic chronic lymphocytic leukemia (37, 51, 75). Nitrogen mustard (53, 59), TEM (37, 40, 56, 59, 62, 75), Thio-TEPA (63), and CB-1348 (37, 53, 56, 67, 75, 76) have been widely employed. BCM (65) and R-48 (77) were reported to be of benefit to some patients with this disease Responses of individual patients to alkylating agents have been rather unpredictable (60, 69), in some, an extreme bone marrow sensitivity was demonstrated (60) Adrenal cortical steroids have been administered to those with acquired hemolytic anemia or thrombocytopenic purpura complicating lymphocytic leukemia (37, 40, 56).

Moeschlin emphasized that demecolcine is contraindicated in the treatment of patients with chronic lymphocytic leukemia, since the drug sometimes produces granulocytopenia or severe exacerbations of the disease (40).

Malignant lymphomas—Roentgen irradiation is still considered the best treatment for malignant lymphoma A voluminous number of clinical reports have appeared during the past few years, however, attesting to the success of drug therapy in keeping patients relatively free of symptoms over considerable periods of time.

Diamond listed the following indications for the use of chemotherapeutic

some sarcomas (102). Patients with rhabdomyosarcoma were also benefited by adenopterin (30). Reese *et al.* reported that TEM given orally, intravenously, and intra-arterially (carotid) in conjunction with radiation therapy seemingly reduced the required dose of radiation and consequently the danger of radiation damage in the treatment of patients with retinoblastoma (103).

Gynecologic cancer.—Li *et al.* (104, 105) reported remarkable improvement of three women with metastatic choriocarcinoma and one with chorioadenoma destruens following the intermittent administration of methotrexate in massive doses, ranging from 15 to 25 mg., daily for five days Metastatic nodules in the lungs diminished greatly, and the urinary gonadotropin titer progressively decreased. Massive doses of methotrexate also brought about a reduction of urinary gonadotropin titer and regression of metastatic pulmonary masses in a patient with choriocarcinoma, observed by Holland (106). In a follow-up report, Li *et al.* documented three additional patients with choriocarcinoma who responded to treatment with methotrexate (107). Five of six women were in clinical remission from three to 23 months. Two exhibited no evidence of residual disease Repeated courses of the drug were followed by unequivocal evidence of tumor regression and a drop in gonadotropin titer. One patient died, apparently from drug toxicity, after regression of the tumor. Japanese investigators reported that nitromin likewise induced objective improvement in patients with choriocarcinoma (64, 108).

Women with ovarian carcinoma were afforded temporary but worthwhile palliation by treatment with a number of alkylating agents after the disease could no longer be controlled surgically or by irradiation (58) Thio-TEPA (63, 76, 81, 109, 110), CB-1348 (111), TEM (62), and E-39 (112) have reportedly proved useful. There appears to be no evidence that the course of ovarian cancer was influenced by changes in hormonal environment (113). On the assumption that cancer formation and subthyroid states are closely related, Loeser gave thyroid hormone to patients with carcinomas of the ovary and uterus. A delay of postoperative recurrence and significant palliation were observed (114).

Cancer of the breast, lung, testis, thyroid—In the treatment of patients with cancer of the breast, major efforts have been concentrated upon ablative surgery, roentgen irradiation, radioactive isotopes, and hormones (115 to 120), less attention has been directed toward chemotherapy. Recent reports indicate that the use of chemical agents is not so effective as controlled alterations of hormonal environment of the tumor (121) Nitrogen mustard and other alkylating agents are being increasingly employed, however, in the management of effusions in the pleural and peritoneal cavities (122, 123). Schell & Hall report that four of five patients with inoperable adenocarcinoma of the breast were benefited by TEM and Thio-TEPA (124). Bateman & Carlton treated four patients by simple mastectomy to remove

responsive to most of the antitumor chemotherapeutic agents, including sarcolysin (80), R-48 (77), CB-1348 (76), TEM (62), and nitrogen mustard (60). At the Conference on Alkylating Agents it was the consensus that, in general, the alkylating compounds were ineffective (58). The agent, 4,4'-stilbenedicarboxamidine di(β-hydroxyethanesulfonate) (Stilbamidine Isethionate) seemed too toxic for clinical use (95, 96). Urethan continued to be the only "specific" drug of value (93 to 96).

Although adrenocortical steroids did not produce objective changes in bone lesions of patients with multiple myeloma, these hormones consistently alleviated bone pain (95). In addition, the euphoria induced by the steroids during their administration was subjectively beneficial. Steroids also ameliorated the symptoms and produced a fall in the urinary calcium values of these patients during hypercalcemic crises (95). Kenny & Moloney, however, did not find cortisone or ACTH helpful (96). Kabakow & Spencer reported that mytatrienediol, a mildly estrogenic agent, afforded striking relief of bone pain and reduced hypercalcemia and urinary calcium excretion without changing the serum electrophoretic pattern and bone marrow morphology (97).

Cancer in children.—The use of chemotherapy in the treatment of children with cancer, exclusive of the leukemias and lymphomas, has not been particularly successful. Patients with a wide spectrum of malignant neoplasms have been afforded varying degrees of palliation by a number of antimetabolites, polyfunctional alkylating agents, and antibiotics, though consistent responses have been conspicuously limited (98).

Bodian and his co-workers (99, 100) have continued to report from London that massive doses of vitamin B_{12} produced regression of neuroblastomas in a significantly high percentage of children, a favorable response was observed in 19 of 38. Of the first 29 treated, 15 obtained good results. Of these 15, 10 were alive in remission from 14 months to 6½ years after institution of therapy. The response was definitely correlated with age, with few exceptions, regression of the tumor was restricted to children whose symptoms appeared during the first year of life. Adjustment of vitamin B_{12} dosage on the basis of body weight made no appreciable difference in the response. Many of these patients were treated by radiation and surgery, in addition to vitamin B_{12}. Similar results from vitamin B_{12} therapy have not yet been reported from American sources.

Chloroquine mustard elicited dramatic improvement in two of five children with disseminated neuroblastoma (101). Folic acid antagonists also exhibited some beneficial activity against this tumor (30). Russian workers observed temporary objective effects upon Ewing's tumor following the administration of sarcolysin to children with this disease (80, 89). Those with metastatic Wilms' tumor received definite palliation from treatment with actinomycin-D (30, 90, 102). In addition, actinomycin-D produced noteworthy changes in the biologic behavior of rhabdomyosarcoma (30) and

under treatment with TEPA and Thio-TEPA (137) Of 14 patients to whom Gumport *et al.* gave Thio-TEPA, five exhibited pronounced objective improvement lasting from a few weeks to a few months (138).

Palliative chemotherapy.—Southam calculated that, on the average, each doctor in the United States has a permanent case load of three incurable cancer patients and, further, that 80 per cent of all incurable cancer patients can expect no worthwhile effect from any type of systemic chemotherapy (139). In the absence of a specific curative agent, chemotherapy for patients with malignant disease must be considered only palliative.

Palliation has been defined as "amelioration of symptoms without affecting the course of the disease" (140) Southam broadened the meaning of the term to include the prevention of impending complications with a minimum of iatrogenic trauma and toxicity (139). Bierman introduced the concept of "arrestive" therapy, by which the malignant process is rendered inactive, stopped or delayed, without actually being cured (140).

In the clinical care of patients in the terminal stages of malignant disease, the prolongation of the period of enjoyable and useful life has been set as a goal (141, 142). The philosophical problems accompanying palliative therapy, such as those pertaining to "restrictions imposed by considerations of personality and of the dignity of man, especially when the laboratory findings so clearly indicate a logical, although divergent, course of procedure" (143), have beeen recognized editorially (144). The point of view of the patient's family has been disturbingly told in the anonymous article, "A Way of Dying," which recently appeared in *The Atlantic Monthly* (145).

The nature and extent of disturbances produced in patients by the presence of various forms of widespread cancer have been covered by Zubrod in the preceding *Annual Review of Medicine* (146), by Gellhorn (147), and in a panel discussion (148). Such considerations have provided the necessary biologic orientation for the care of these patients

Convincing evidence that the intracavitary use of alkylating agents is valuable in the control of malignant serous effusion has accumulated (110, 124, 126, 149, 150, 151) In a summary of his experiences, Weisberger reported that nitrogen mustard introduced into serous cavities (intrapleural, intraperitoneal, and intrapericardial) controlled the effusion of 56 of 88 patients, in 43 the fluid did not reaccumulate (150). Treatment with alkylating agents possessed practical advantages over that with radioisotopes· the cost to the patient was less, no radiation hazard was associated, and no special equipment or facilities were necessary. The clinical results compared favorably with those achieved by treatment with radioactive colloidal gold (150, 152). Of interest was the report by Chambers that in 17 of 20 patients pleural effusions incident to malignant neoplasms were satisfactorily controlled with instillations of talc into the chest cavity (153). It was his opinion that the production of obliterative pleuritis, whether by talc or by alkylating agents, was responsible for the control of the effusion.

Hypercalcemia and hypercalciuria in patients with malignant neoplastic

grossly ulcerated tumors, together with local injections of Thio-TEPA (125) These patients were not considered curable. Remissions of five to 15 months were obtained by the combined use of the two methods

Patients with carcinoma of the lung received temporary palliation from treatment with alkylating agents (58, 126). Nitrogen mustard was the most effective (127), producing subjective improvement in 50 to 60 per cent of these patients and objective evidence of tumor regression in 30 to 40 per cent (60). Thio-TEPA and TEM were somewhat less beneficial than nitrogen mustard (127). Busulfan (128) and nitromin (64) were also palliatively active in patients with lung cancer. Chemotherapy was useful in the care of those with widely disseminated disease, radioresistant tumors, exhaustion of radiation tolerance of skin or lungs, intractable radiation sickness, and particularly the vena caval syndrome (127). The majority of patients with symptoms of superior vena caval compression were relieved following the administration of alkylating agents (60, 127)

Testosterone therapy was followed by temporary disappearance of metastatic lesions in two patients with embryonal carcinoma of the testis (129). Massive doses of methotrexate and 6-mercaptopurine, however, failed to produce significant improvement of five patients (107).

Larionov and his colleagues reported that sarcolysin exerted pronounced beneficial effects upon seminoma and its metastases (80, 89, 130) In 18 of 24 patients this drug induced regression of the size of the masses, though not disappearance of tumor elements histologically (130). The responses were so consistent that administration of sarcolysin was suggested as a test to differentiate seminomas from teratomas and chorionepitheliomas, upon which it had no apparent effect

On the possibility that the pituitary thyrotropic hormone may serve as a promoting factor in carcinoma of the thyroid (131), Crile recommended that most patients with inoperable cancer of this gland be given desiccated thyroid as a trial measure prior to radioiodine therapy (132, 133) He further suggested the administration of thyroid hormone to prevent recurrences following operations for thyroid carcinoma. Thomas employed desiccated thyroid, thyroxine, and L-triiodothyronine as pituitary thyroid-stimulating hormone (TSH) depressants in the care of patients with the disease (134, 135). This approach appears to have merit, though its further clinical validation must be awaited.

Malignant melanoma.—The bleak outlook for patients with disseminated [illegible]

[illegible]

to 16 and intravenously to six patients with metastatic melanoma; it was hoped that this compound, being a phenylalanine analogue, would exhibit enhanced selectivity for the tumor. Objective evidence of limited benefit, however, was observed in only two of the 22 (136). Tullis reported that three of 15 patients with widespread malignant melanoma obtained remissions

implications of their observations, however, have not yet been substantiated in clinical experience.

The concomitant administration of a folic acid antagonist and a purine antagonist to children with acute leukemia led to added toxicity without any demonstrable summation of therapeutic benefit (30, 37, 165). A combination of 6-mercaptopurine with either azaserine or DON was given to these children by one cooperative group (40). A report of the results is still unavailable. Preliminary trials indicated that, although azaserine (166) or DON (157) given alone exhibited no significant therapeutic effect, the combination with the antipurine drug may prolong the duration of remissions in some patients (35, 37, 167). Simultaneous treatment with TEM, aminopterin and 6-mercaptopurine did not materially prolong the lives of 53 patients with inoperable bronchogenic carcinoma which was unsuitable for roentgen irradiation, though a "small palliative effect" was claimed (168).

Chemotherapy as an adjunct to radiotherapy.—Bane, Conrad & Tarnowski, in a thoughtful review, discussed the history, the theories, and results of animal investigations and clinical experiences concerned with combined chemical and ionizing radiation therapy for malignant tumors (169). Three major avenues of approach were described: (*a*) attempts to obtain synergism from a combination of radiation and agents having antitumor activity; (*b*) attempts to increase radiosensitivity of tumors by noncarcinostatic agents; and (*c*) attempts to increase radiation doses to tumors by means of carriers, secondary radiators, and thermal neutron capture. Shapiro (170) and Kligerman & Shapiro (171) reported a series of experiments which demonstrated that radiation given concurrently with a "multi-combination" chemotherapeutic attack, selected for interference with the energy requirements of the cancer cell, produced materially better antitumor effect than either modality alone.

Loken used porphyrins as modifiers of the effect of roentgen rays in the treatment of 51 patients with relatively radioresistant, inoperable cancers (172). The response of one-third or more of the neoplasms was appreciably better than was expected. Evaluation is difficult, through studies of roentgen irradiation combined with the administration of the copper complex of hematoporphyrin appear encouraging. Some evidence that actinomycin-D increased the radiosensitivity of Wilms' tumor and of rhabdomyosarcoma in children has also been reported (173)

Thomas points out that radiation produces a localized chemical effect which can be fairly well controlled both as to extent and degree of severity (174). This, combined with anticancer chemicals which act upon the various metabolic functions of the cell, should augment the desired action of either. Thomas gave chemical compounds to over 100 patients who were treated primarily with irradiation, with still inconclusive results The drugs were CB-1348, busulfan, 6-mercaptopurine, aminopterin, and testosterone, alone or in combinations When given to animals with transplanted tumors or Ehrlich ascites tumors, the same drugs permitted a 50 per cent reduction of

disease may produce life-threatening alterations of various physiologic functions (154, 155). Chemotherapeutic agents, including nitrogen mustard (60), DON (156, 157) and mytatrienediol (97), as well as cortisone and hydrocortisone (158), temporarily reduced hypercalcemia and hypercalciuria. Presumably, this palliation was produced by inhibition of tumor growth in bones. As Myers points out, however, other mechanisms cannot be excluded, since hypercalcemia also develops in the absence of demonstrable bone metastases (158).

Although McCarthy had reported previously that palliation and remission of symptoms and signs of disseminated cancer of various types were induced by combined corticosteroid and nitrogen mustard therapy (159), a more recent study of 68 patients by Jones failed to reveal comparable results from concomitant treatment with nitrogen mustard, prednisone, and chlortetracycline (160). Large doses of amethopterin, given intravenously, produced objective responses in 20 per cent and subjective improvement in 38 per cent of patients with malignant disease (161). Reports such as this, and the demonstration already cited, of the effectiveness of massive doses of amethopterin for choriocarcinoma encourage further investigations of intensified antimetabolite therapy for solid tumors, at present generally unresponsive to conventional dose regimens.

Prophylactic chemotherapy.—The application of chemotherapeutic principles to cancer prophylaxis has been limited. Of particular interest, therefore, are the ingenious investigations of enzyme activity with reference to cancer of the bladder, by Boyland *et al.* (162). They proposed to inhibit the urinary β-glucuronidase of patients with cancer of the bladder by treatment with 1:4-saccharolactone and related compounds. Oral administration of this drug every 6 hr. was followed by a 90 per cent reduction of enzyme activity in the urine. Since the liberation of free carcinogenic aminophenols in the urine of patients with cancer of the bladder is dependent upon the action of the enzyme β-glucuronidase, according to these workers, such liberation would be largely controlled. Treatment with 1:4-saccharolactone is recommended for men who are exposed to carcinogenic aromatic amines while working in chemical industries. It is also being given to patients following removal or destruction of a cancer of the bladder, in an attempt to prevent recurrence or generation of a new tumor.

Combination chemotherapy.—The fundamental principles and experimental data which underlie the treatment of patients with malignant disease by means of combinations of chemical compounds have been critically reviewed by Goldin & Mantel (163). By sequential or concurrent blockage of metabolic pathways, combined drugs are intended to damage the cancer cell through several mechanisms. The objective and approach of these studies of synergism and potentiation of chemotherapeutic compounds are comparable to studies on antimicrobial therapy (164). In an addendum, Goldin and Mantel presented summaries, with pertient comments, of 24 important investigations of combination chemotherapy for tumors in animals. The

obtained from veins draining cancers of the lung and gastrointestinal tract contain tumor cells, pointed to the possibility of preventing the establishment of metastases in patients undergoing surgical treatment (186). Chemotherapy was advocated on the theory that any remaining tumor cells, whether at the site of the surgery, in the circulating blood, the lymphatics, or in distant organs, may thus be devitalized. The results reported to date do not permit a decision as to the effectiveness of this procedure. Moore concludes that only clinical studies with proper statistical design and subject to continuous review should be undertaken at this time (187).

Prophylactic treatment at the time of operation upon patients with cancer has been proposed by Cole and his associates (188). In animal experiments, they observed a pronounced reduction in "takes" of cancer cells injected into rats when an anticancer agent was given at the same time or shortly thereafter. Nitrogen mustard and Thio-TEPA were both effective Conclusions based upon a trial of this technique in 65 patients were incomplete. The procedure appeared to have merit, though the number of postoperative complications was increased.

Other facets of this therapeutic approach have also been explored (189, 190, 191). For example, animal studies indicated that chemotherapeutic response was inversely related to the amount of tumor tissue present (192).

Perhaps the most interesting program yet initiated for the use of chemopeutic agents combined with surgery was proposed by Ryan *et al.* (193, 194). By their technique, a pump oxygenator is employed to perfuse an isolated limb or area of the body with a chemotherapeutic drug. Intra-arterial injection of nitrogen mustard was reported by Klopp *et al.* in 1950 (195), and more recently by other investigators, including Davis *et al* (196) and Krakoff & Sullivan (197). The use of the "heart-lung" machine for extracorporeal perfusion, however, offers much greater possibilities. Following trials on animals, Creech and his associates treated a number of patients with solid tumors and melanomas in different sites by this procedure. The initial responses varied The method is advantageous in that it minimizes systemic toxicity (193, 194). A higher concentration of HN2 and TEM in tumor tissue has been found after intra-arterial administration proximal to the tumor than after intravenous injections (198)

Experimental design in clinical evaluation —The problems involved in the treatment of patients with cancer by means of highly toxic, relatively untried chemotherapeutic agents have been critically examined (30, 199, 200). Zubrod (201) listed prerequisites to the clinical use of new drugs as follows: (*a*) informed consent of the patient, (*b*) availability of adequate data from animal studies to show the limits of toxicity and to indicate the possibility of antitumor activity in the patients, (*c*) broad experience of the principal investigator in drug trials; (*d*) adequacy of staff, facilities, and attitudes; and (*e*) properly designed study.

For the clinician, proper therapeutic trials involve basic statistical orientation (165, 202), and objectivity and precision of observation techniques

the usual amount of radiation required for control of the tumors. Variations in the mode of administration of the chemical compounds was an important part of the study. Patients with inoperable carcinoma of the pelvic region—from the bladder, rectum, colon, or ovary—were materially relieved of pain by perfusion of the area through the aorta with nitrogen mustard a short while before they received external irradiation.

Clinical experience with simultaneous irradiation and chemotherapy appears to be increasing. As mentioned earlier in this review, Reese and his group combined an alkylating agent (TEM) with radiation in the treatment of children with retinoblastoma (103). The results were better than those obtained by methods previously employed. In addition, the dose of radiation was reduced by more than one-half, thus minimizing the danger of serious local radiation damage. Finally, treatment in circumstances hitherto considered unfavorable for radiation alone appeared feasible. Following the administration of both nitrogen mustard and roentgen ray therapy to 226 patients with inoperable carcinoma of the lung, Krabbenhoft & Leucutia observed a slight improvement in the survival rate within the first year (175).

The radiobiological evidence that the oxygen supply of the cell affects radiosensitivity has been examined by Gray (176). Churchill-Davidson *et al.* administered radiation with oxygen under pressure to 35 patients who were believed to have practically no chance of cure by conventional radiotherapeutic methods (177). They were placed in a specially constructed chamber, under three atmospheres of oxygen during the radiotherapy. General anesthesia was used and myringotomies were performed prophylactically. These authors conclude cautiously that the initial response of the tumors was better than would otherwise have been expected.

Mitchell summarized the extensive research on the use of noncarcinostatic chemical agents designed to act as radiosensitizers (178, 179). He also evaluated the results of experience with Compound I. tetra-sodium 2-methyl-1:4-naphthohydroquinone diphosphate (Synkavit) given in conjunction with radiotherapy to 1370 patients. It was concluded that the intravenous administration of the drug had a "small but useful effect as a clinical radiosensitizer" on 203 with inoperable carcinoma of the bronchus.

In animal experiments, a noncarcinostatic chemical compound, S, β-aminoethyl-isothiouronium bromide hydrobromide (AET), significantly reduced toxicity of both roentgen rays (180) and alkylating agents (181, 182).

Chemotherapy as an adjunct to surgery.—A comprehensive, planned study of the combined use of chemotherapy and radical surgery for cancer has been activated by the Adjuvant Chemotherapy Study Group under the auspices of the clinical panel of the Cancer Chemotherapy National Service Center. A brief résumé of the rationale of this program is given by Moore (183, 184). In experimental work, he found that chemotherapeutic agents were effective against unestablished tumors, although they were ineffective in destroying the same type of established tumors (185). This observation, combined with the report that approximately one-half the samples of blood

of activity, the largest being the routine empirical screening for antitumor effects of synthetic chemicals, antibiotic culture filtrates, plant extracts, and steroids

Following extensive animal studies and scrupulous planning, supervised by both pharmacologists and clinicians, preliminary tests for toxicity in human subjects are made of potentially effective agents in medical centers. To insure the accumulation of statistically adequate data in the most efficient and time-saving manner, definitive clinical trials are conducted by the voluntary, cooperative groups. Each study adheres strictly to a protocol which (*a*) defines objective criteria for diagnosis and measurement of response and (*b*) prescribes treatment schedules and statistical control. In 1958, about 20 groups, representing roughly 165 hospital services, were conducting cooperative studies of more than 40 separate compounds in approximately 1600 patients.

Both empirical and basic research are pursued in this program. Among the current activities are investigations of the mechanism of action of various chemical agents; research to discover other means of inhibition of growth of cancer cells, studies of the physical and chemical characteristics of organic cells in an effort to determine the essential differences between normal and cancer cells; and studies of the biology of animal tumors, of cancer cells in tissue cultures, and of human tumors in heterologous hosts. The magnitude and diversity of published reports preclude inclusion herein of even a cursory survey of these investigations, they require a separate review and bibliography.

An end-result appraisal program has been created by the Service Center to correlate responses of patients to total treatment in terms of length of survival. It is expected that the final data will also provide important retrospective and prospective statistical information concerning the natural history of human cancer.

With the exception of such tremendous programs as the atomic energy studies, there are probably few research disciplines of the magnitude of the National Chemotherapy Program. The cooperation of industry, government agencies, private research foundations, medical schools, hospitals, and independent investigators has helped to make possible this remarkable expansion. Most important, the research grant method has proved effective in precluding bureaucratic interference with freedom of scientific investigation It is believed that this program, through its financial resources and the coordinated activities of its network of participants, will lead to the development of new therapeutic instruments and techniques, and the discovery of more effective drugs for cancer control

(203). Examples of coordinate grid mapping to identify the site and size of lesions (204), and detailed methods of recording clinical data have been described (205). In children with acute leukemia, assessment of the effect of treatment has been based upon criteria which systematically considered the bone marrow findings, the peripheral blood picture, evidence of leukemic infiltration, and the subjective status of the patient (206, 207, 208). Gellhorn classified objective therapeutic response in terms of (*a*) modification of tumor progression (anatomical, biochemical, and functional); (*b*) time parameters (onset of effects, duration of remissions, survival); (*c*) reproducibility of effects; and (*d*) toxicity of the agents (209, 210). The interpretation of clinical data has been further complicated by a number of factors, such as spontaneous regression of tumors (211), individual biologic variability (212), and interactions between the tumor and host (14, 213).

Collins (214, 215) and others (216) studied the growth rate of tumors, especially in children, in relation to prognosis. Their observations added support to the fact that more extensive and definitive information of the natural history of individual types of cancers is necessary for precise assessment of the variations introduced by therapy (40, 217, 218, 219). Several approaches to the analysis of data from therapeutic trials have been investigated (91, 220, 221). From statistics, Hammond estimated that five-year surivival rates may be improved by about 7 percentage points through earlier diagnosis alone, but about 7 percentage points through better treatment alone, and by about 16 percentage points through earlier diagnosis and better treatment (222).

The National Chemotherapy Program

The history, basic framework, and mechanism of this program have been reviewed in a comprehensive manner by Endicott (223, 224). The Cancer Chemotherapy Committee of the National Advisory Cancer Council was created in July, 1954. The American Cancer Society and the Damon Runyon Memorial Fund for Cancer Research became cosponsors with the National Cancer Institute in 1954, the Cancer Chemotherapy National Service Center (CCNSC) was established in April, 1955; the Cancer Chemotherapy National Committee was organized in June, 1955, and advisory panels in Chemistry, Screening, Pharmacology-Biochemistry, Clinical Studies, and Endocrinology were appointed during 1955 and 1956 Among other cooperating agencies are the Food and Drug Administration, the Atomic Energy Commission, and the Veterans Administration Industrial participation is promoted through the efforts of a special subcommittee. The program is supported largely by congressional appropriations, though grants from other agencies are also available. In 1955 the appropriation by the Government amounted to $5,000,000, in 1958 this was increased to $25,000,000

Sharing in the National Chemotherapy Program are hundreds of individual investigators, whose work is voluntarily coordinated when necessary. This voluntary cooperative approach has been established in several areas

of activity, the largest being the routine empirical screening for antitumor effects of synthetic chemicals, antibiotic culture filtrates, plant extracts, and steroids.

Following extensive animal studies and scrupulous planning, supervised by both pharmacologists and clinicians, preliminary tests for toxicity in human subjects are made of potentially effective agents in medical centers. To insure the accumulation of statistically adequate data in the most efficient and time-saving manner, definitive clinical trials are conducted by the voluntary, cooperative groups. Each study adheres strictly to a protocol which (*a*) defines objective criteria for diagnosis and measurement of response and (*b*) prescribes treatment schedules and statistical control. In 1958, about 20 groups, representing roughly 165 hospital services, were conducting cooperative studies of more than 40 separate compounds in approximately 1600 patients.

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TABLE I

Chemotherapeutic Agent	Selected and Current References
Nitrogen mustard (mechlorethamine hydrochloride; HN2; Mustargen; Embichin)	25, 26, 30, 37, 59, 60, 78, 127, 150, 152, 159, 160, 175, 197, 225
methyl *bis*-(β-chloroethyl)amine hydrochloride	
Chlorambucil (CB-1348, Leukeran)	11, 30, 37, 40, 67, 68, 75, 76, 82, 83, 86, 87, 111, 226
p-N-N-Di-(2-chloroethyl)-*p*-aminophenylbutyric acid	
Nitromin (Mitomen, Nitro-lost; MBAO; N-oxide mustard)	
Methyl-*bis*-(β-chloroethyl)amine N-oxide hydrochloride	30, 48, 64, 227
Phenylalanine nitrogen mustard (racemic form: sarcolysin; L-isomer: CB-3025; Melphalan; PAM)	
p-Di-(2-chloroethyl)aminophenylalanine	80, 88, 89, 130, 136
Novoembichin	
2-chloropropyl-di-(2-chloroethyl)amine hydrochloride	26, 225
Dopan	
4-methyl-5-(*bis*-(β-chloroethyl)-amino)) uracil	26, 89, 225
SM-1	
1,2-*bis*-(β-chloroethylthio)ethane	228
Hemisulfur mustard (HSM; hemi-H)	
2-chloro-2'-hydroxydiethyl sulfide	30, 151
R-48 (erysan; chloronaftine; CB-1048)	
N, N-Di-(2-chloroethyl)-β-naphthyl amine	30, 77, 86
BCM (degranol, mannitol nitrogen mustard, degranolchinoin)	
1,6-*bis*(2-chloroethylamino)-1,6-deoxy-D-mannitol dihydrochloride	65
Chloroquine mustard	
7-chloro-4-((4-*bis*(β-chloroethyl)amino-1-methyl butyl amino)) quinoline	101
Triethylene melamine (TEM)	11, 25, 30, 37, 40, 56, 59, 61, 62, 75, 78, 103, 124, 127, 168
2,4,6-triethyleneimino-S-triazine	
Triethylene phosphoramide (TEPA)	25, 30, 37, 137
Triethylene thiophosphoramide (thio-TEPA; TSPA)	25, 30, 37, 63, 76, 81, 85, 109, 110, 124, 126, 127, 137, 138, 196
ODEPA	
N-3-oxapentamethylene-N',N''-diethylene phosphoramide	110
OPSPA (MSPA)	
N-3-oxapentamethylene-N', N''-diethylene thiophosphoramide	229

TABLE I—*Continued*

Chemotherapeutic Agent	Selected and Current References
Busulfan (Myleran; G. T. 41) 1,4-dimethanesulfonoxybutane	25, 37, 40, 53, 56, 57, 59, 61, 69, 70, 71, 72, 84, 128
Dimethyl myleran (CB-2348)	230
Nonane 1,9-dimethanesulfonoxynonane	25, 231
Bayer E-39 2,5-*bis*-(1-aziridinyl)-3,6-dipropoxy-*p*-benzoquinone	66, 112, 232
Aminopterin 4-amino-pteroylglutamic acid	29, 30, 37, 168
Amethopterin (Methotrexate) 4-amino-N[10]-methylpteroylglutamic acid	11, 17, 27, 29, 30, 35, 36, 37, 40, 46, 51, 59, 104, 105, 106, 107, 161
6-mercaptopurine (mercaptopurine; 6-MP; purinethol)	8, 15, 27, 28, 29, 35, 36, 37, 40, 44, 52, 59, 167, 168
6-chloropurine (6-CP)	28, 29, 35, 37, 52, 233
Thioguanine 2-amino-6-mercaptopurine	28, 35, 37, 39, 233
8-azaguanine (guanazolo; azan) 2-amino-6-hydroxy-8-azopurine	28, 29, 30, 234
5-fluorouracil (5-FU; RO 2-9757)	235
Actinomycin C (sanamycin C)	30, 234, 236, 237
Actinomycin D	11, 30, 173, 234, 237, 238, 239, 240
Azaserine (seryl; P-165) O-diazoacetyl-L-serine	11, 29, 35, 37, 40, 51, 166, 167, 173
DON 6-diazo-5-oxo-L-norleucine	11, 37, 156, 157
Carzinophilin	—
Mitomycin	241
Urethane (urethan) Ethyl carbamate	30, 37, 56, 59, 93, 94, 95, 96
Demecolcin (demecolcine, Colcemid, Omain) Deacetylmethylcolchicine	30, 40, 57, 73, 74, 242

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DISEASES OF THE NERVOUS SYSTEM[1]

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Viral Encephalitis

The viral encephalitides constitute an ever present problem in all parts of the world. Two recent symposia have extended current knowledge of these disorders (1, 2). Many aspects of pathology and of pathogenesis have been clarified, problems of epidemiology solved, etiologic diagnosis of clinical syndromes established, and certain advances in control, prevention, and treatment have been delineated.

Those encephalitides which are most important from an epidemiological point of view are the arthropod-borne ones, and these can be divided into two groups—the tick-borne and mosquito-borne infections (3). Of the former, the most important virus is that associated with Russian spring-summer encephalitis and similar syndromes found throughout the Eurasian continent. In the Far East, the vector for this is said to be the tick *Ixodes persulcatus*, and in Central Europe the tick *Ixodes ricinus*. Apparently the ticks themselves can be the ultimate reservoir of the virus, which is transmitted through the eggs from one generation of ticks to another The second group of arthropod-borne infections are those carried by mosquitoes The most important vector for the Western equine encephalitis virus is the mosquito *Culex tarsalis*, the preferred hosts of this mosquito are birds, but when an inadequate number of bird hosts are available the mosquitoes may bite horses or other large animals. The natural vector for the virus of Eastern equine encephalitis is the mosquito *Culisetta melanura*, which bites predominantly birds, then horses and, rarely, man Presumably, this virus may pass from bird to bird without mosquitoes. The vector for the virus of St. Louis encephalitis is the mosquito *Culex tarsalis* in the Western United States, and *Culex pipiens* in the Middle West and Ohio Valley The mosquito of importance for transmission of Japanese B encephalitis is *Culex tritaeniorhynchus;* this mosquito also predominantly bites birds and larger animals No transovarian passage of virus from one generation of mosquitoes to the next has been demonstrated, and one of the chief questions regarding the mosquito-borne infections is how the viruses survive during the winter months. It has been suggested that the virus may persist in one form or another in birds during winter and become available again to mosquitoes during the proper period of the year, that migratory birds may carry the virus from tropical and subtropical regions to temperate zones, or that mites may serve as hosts for the overwintering of the virus.

[1] The survey of the literature pertaining to this review was completed in July, 1958

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The first, a cooperative project designed to involve about 25 research medical centers, is aimed at the evaluation of medical and surgical measures in the treatment of subarachnoid hemorrhage and intracranial aneurysms. In the second, a number of research teams have joined forces to evaluate the effect of anticoagulants in the treatment and prevention of cerebrovascular accidents. It was felt, however, that an important preliminary measure to these studies would be an adequate validation of present-day criteria for the classification and diagnosis of cerebrovascular diseases. This has been published under the auspices of an *ad hoc* committee under the chairmanship of C. H. Millikan (11).

For a thorough understanding of the pathological alterations which occur in cerebrovascular disease, factors influencing the cerebral collateral circulation have been analyzed in the terms of local changes in oxygen availability, temperature, pH, electrocorticogram, and steady potential (12). Adjustments in collateral blood flow following cerebrovascular occlusion appear to be mediated by vessels of all sizes, from the large arteries of the circle of Willis to the small arterioarterial anastomoses of the cortex measuring 50 to 250 μ. These small arterial anastomoses form multiple connections between arterial trunks and permit wide readjustments in local blood flow when an artery is occluded.

Occlusion of the internal carotid artery is now recognized as one of the most important entities of cerebrovascular disease from a statistical point of view, and many important investigations have been reported from the study of this syndrome (13). Temporary digital carotid artery compression has been shown by Webster & Gurdjian to be a valuable test for identifying occlusive cerebrovascular disease, particularly when hemiplegia or hemiparesis is present or developing (14) When syncope is induced by temporary digital carotid compression on the side of the paralysis, contralateral carotid occlusive disease is probable; occlusion of an anterior cerebral artery is usually accompanied by syncope on contralateral compression. Occlusion of the carotid artery may also be diagnosed by ophthalmodynamometry (15, 16, 17). By this procedure the pressure in the central artery of the retina (a branch of the ophthalmic artery, which is the first sizeable branch of the internal carotid) is measured. This procedure is more reliable than palpation of the carotid and is safer than either digital compression or arteriography. There has been recent optimism regarding various types of surgical treatment of this important syndrome following the first report by Eastcott, Pickering & Rob of reconstruction of the internal carotid artery in a patient with attacks of hemiplegia (18) Successful results have been reported with thromboendarterectomy (19), anastomosis of the external carotid artery to the internal carotid artery above the thrombosis (20, 21), and arteriovenous bypass graft using a specially designed dacron tube The most extensive and encouraging report is that of Fields, Crawford & DeBakey (22), who have operated on 31 of 42 patients with either partial or complete occlusive disease. Thromboendarterectomy (opening the artery and removing a localized sec-

The clinical features and pathological alterations of the viral encephalitides are fairly well known, but the incidence and characteristics of the sequelae are not as clearly understood. Finley & Longshore have followed 750 patients who had acute infections with either Western equine or St. Louis encephalitis in the Central Valley of California during the period from 1945 to 1957 (4). The incidence and severity of sequelae have been found to be related directly to age. The younger the patient, the more serious the acute illness and the more likely he is to have severe and permanent residuals. A large proportion of infant patients have convulsions during their acute illnesses, and the sequelae in infants consist of motor impairment (pyramidal, extrapyramidal, and cerebellar), behavior disturbances, retardation, and convulsions (5). In adults the sequelae usually consist of subjective complaints such as nervousness, irritability, easy fatigability, headache, and tremulousness, and these symptoms usually disappear, leaving no residuals. The sequelae of St. Louis encephalitis are less frequent and less severe than those of the Western equine variety, but this may in part arise from the fact that the St. Louis encephalitis is rarely observed in the younger age group. Eastern equine encephalitis runs a much more fulminating course than the other varieties and, as might be expected, the sequelae are much more severe in those patients who survive. Of 50 cases studied by Feemster, 16 survived the acute illness; eight of these were under five years of age and six had very severe sequelae (6). In older children the residuals were less severe, and of four patients over the age of 40 who survived, only one manifested mild sequelae. The residuals of those who had the illness in childhood consisted of mental retardation, strabismus, convulsions, lack of emotional control, hemiplegia, impaired vision, partial deafness, and speech disorders.

The immediate and serious complications of the 1957 epidemic of Asian influenza were quite rare considering the large number of individuals who have been reported to have contracted the illness. There have, however, been a few individual but significant reports of neurological complications of this disease. Encephalitic manifestations were definite clinically and confirmed by the presence of cerebrospinal fluid abnormalities, and the relationship to the influenza A type virus was established by rise in antibody titer in the hemagglutination-inhibition test against the Asian influenza virus. One patient had definite residual manifestations consisting of an athetoid tremor, but the time has been too short to evaluate more permanent sequelae (7 to 10).

Cerebrovascular Diseases

Cerebrovascular diseases constitute perhaps the most important group of organic affections of the central nervous system, and there has been a recent increase of interest in the study of their clinical and pathological manifestations, diagnosis and treatment. Two nation-wide studies on specialized aspects of cerebrovascular disease have been initiated under the auspices of the National Institute of Neurological Diseases and Blindness

produces a localized impairment of neuronal function, with resultant motor and sensory deficit (26). During the stage of paralysis metabolic utilization of oxygen is decreased. Administration of glucose restores normal functional activity and oxygen consumption to the area of hypoglycemia. If hypoglycemia is sufficiently prolonged, however, the changes become irreversible and necrosis of nerve cells occurs

Parkinsonism

Surgical measures for the relief of Parkinsonism and associated hyperkinetic disorders were the subject of two symposia during 1958, neither of which has been published as yet (27, 28). The results of such procedures in a large number of patients, however, are now available in the literature (29). Cooper & Bravo reported a five-year follow-up study of more than 700 operations, and state that the tremor and rigidity of Parkinsonism are relieved in 80 per cent of properly selected cases, with a risk of mortality of 2 4 per cent and of hemiparesis of 3 per cent (30) They have also reported relief of symptoms in conditions such as dystonia musculorum deformans, choreoathetosis, and hemiballismus by means of discrete chemical lesions of the globus pallidus or the ventrolateral region of the thalamus or both Spiegel & Wycis report encouraging results with stereotaxic pallido-ansotomy (31), and Bertrand by a pneumotaxic technique for producing localized cerebral lesions (32). Meyers, Fry and their associates use a focused four-beam ultrasonic apparatus for producing lesions of predetermined geometric size, shape, and position in the human brain for the amelioration of hyperkinetic disorders (33) They report relief of hypertonus with lesions in the ansal region and simultaneous relief of both rigidity and tremor with lesions in the substantia nigra In spite of advances in the surgical treatment of Parkinsonism, however, for the majority of patients a medical approach is necessary With advances in pharmacological treatment, the outlook for patients has improved through the years (34).

"Psychomotor" or "Temporal Lobe" Epilepsy

With advances in the understanding and classification of epilepsy, it is evident that a much larger percentage of cases than was once believed are accompanied by various psychological, sensory, hallucinatory, and vegetative manifestations, which places them in the group of the so called "psychomotor" or "temporal lobe" epilepsies (35, 36) Clinically many of these have olfactory and gustatory accompaniments as well as disturbances of memory and affect (37), and it is apparent that an abnormal discharge in the region of one or both temporal lobes and contiguous structures is responsible for the seizure (38) Ictal emotions, or emotions occurring as part of a seizure and not as reactions to other events of the attack, are most common with lesions below and adjacent to the sylvian fissure Ictal emotions limited to anger and fear occur with epileptic discharges involving the anterior half of either temporal lobe, depression is associated with lesions diffusely distributed in the

tion of the intima containing the obstructing atheromatous mass) was carried out in ten, with complete restoration of circulation in nine, and a bypass graft (insertion of a dacron tube, one end sutured to the uninvolved artery proximal to the lesion, the other to the artery distal to the lesion) was carried out in 21, with restoration of circulation and relief of symptoms in all. The results of all attempts at such surgery have not been universally successful, however, and Lemmen has recently called attention to the limitations of surgical therapy (23). Retrograde flow of blood from the internal carotid artery is not always an index of complete removal of the thrombus, and the procedure should be accompanied by angiography. Furthermore, restoration of the blood flow does not necessarily imply recovery of function, nor does immediate improvement in any way prognosticate a continued improvement

Subarachnoid hemorrhage—In an analysis of the autopsy findings of patients dying from subarachnoid hemorrhage, over a 21-year period at the University of Michigan Hospital, Bebin & Currier found that in all patients in whom death was thought to be caused primarily by the rupture of an intracranial aneurysm there was evidence of intracerebral, intraventricular, or subdural hemorrhage (24) This indicates that death in such cases appears to be the result of hemorrhage into areas other than, but usually in addition to, the subarachnoid space, the most common being intracerebral with or without the associated intraventricular hemorrhage.

Cerebrospinal fluid in cerebrovascular disease.—Careful analysis of the blood and blood pigments in the cerebrospinal fluid is important not only in the diagnosis of subarachnoid hemorrhage but also in the differentiation between cerebral hemorrhage and cerebral infarction, especially if anticoagulant therapy is considered for the latter (25). Absorption spectrophotometric studies of the pigments in xanthochromic spinal fluids aid in the analysis of hemorrhagic fluid and in differentiation between subarachnoid and cerebral hemorrhage and so-called traumatic spinal punctures Oxyhemoglobin, the first pigment to appear after subarachnoid hemorrhage, is a product of hemolysis and may be found within two hours of onset. It increases rapidly, becoming maximal in the first few days, and gradually diminishes over a week or ten days if no further bleeding occurs. Bilirubin, the iron-free derivative of hemoglobin, also appears following the hemolysis of erythrocytes. It is first apparent in two or three days and increases as the amount of oxyhemoglobin decreases It may persist for two or three weeks It is also the pigment present in the spinal fluid in cases of subarachnoid block, the result of transudation from blood plasma, and may be present in the fluid in association with jaundice and liver disease. Although the supernatant fluid is usually clear in association with traumatic punctures, it has been shown that oxyhemoglobin may be found by spectrophotometry if there are more than 12,000 erythrocytes per cubic millimeter

Localized cerebral hypoglycemia—Meyer & Portnoy have demonstrated that in the presence of an area of relative ischemia of the brain, hypoglycemia

patient develops twitching movements of the jaws which increase in frequency and are then followed by a generalized convulsion. Either a temporal lobe or a frontal lobe spike focus has been noted in most cases

Function and Structure of Myelin and Glia

By means of electron microscopy, Finean has demonstrated the layered structure of myelin in which leaflets of bimolecular lipide alternate with thin layers of protein (52) The composition of the lipide layers is complex, but consists mainly of phospholipide, cholesterol, and cerebroside. The diffraction data obtained from myelin of the central nervous system are markedly different from those of peripheral nerves Luse, in studying the formation of myelin in the central nervous systems of mice and rats, also by electron microscopy, has demonstrated that oligodendroglia perform the same function of building myelin in the central nervous system as the Schwann cells perform in peripheral nerves (53) Lumsden, in studying the functional aspects of the glial apparatus, has demonstrated the intimate association of the astrocytic podia with the endothelium of the brain capillaries, and expresses the belief that the blood-brain barrier is a function of glial protoplasm (54). He states that this barrier is not a specific membrane or architectural layer but the whole width of the gellike matrix that extends from the capillary endothelium to the nerve cell body, its axon, and dendrites He states, furthermore, that the difference between unmyelinated and myelinated nerves is quantitative only, since the unmyelinated usually have at least one lamella of myelin. The process of myelination apparently arises from the gradual progressive addition of layers and not to thickening of the individual layers (55). Farquhar & Hartmann have also studied glial structure by electron microscopy and feel that the glia are essential to the metabolic processes of the brain and are not just inert supporting structures (56) The relations of astrocytes to capillaries, together with the structural features of the cells, suggest a nutritive function. Material from the blood stream, after once traversing the capillary wall, can readily diffuse along the astrocytic processes to be distributed to other cellular elements of the brain.

The Reticular Formation

The proceedings of an international symposium on the reticular formation of the brain, held at the Henry Ford Hospital in Detroit in March, 1957, are in press (57). French, one of the participants on the program, has summarized our present knowledge of the reticular formation, including the vast amount of new material presented at the symposium (58) The central brain-stem masses comprising this system are derivatives of a phylogenetically ancient column of spinocerebral neurons which are interposed between sensory nuclei and motor cells Vertebrate encephalization has resulted in tremendous expansion of the rostral end of this structure and has magnified extensively the ramifications of its functions. Implicit in the mediation of these manifold

temporal lobes, while pleasure and unpleasure are principally associated with the posterior temporal lesions. In many cases the pattern of seizure organization suggests an ordered "march" of manifestations originating in the temporal lobes and environs (39). It is apparent, however, from depth recording techniques by Walker and others, that subcortical areas other than the temporal lobes, including the frontal lobes, thalamus, hypothalamus, and basal ganglia, may also be important, casting doubt upon the concept of pure temporal lobe pathogenesis of psychomotor epilepsy and permitting factual explanation of certain failures after temporal lobectomy (40).

At the present time there is no universal agreement on pathological alterations in the temporal lobes and related structures in psychomotor epilepsy, but an increasing number of reports point to histological changes in these areas of the brain, including sclerosis in Ammon's horn and the uncal region (41, 42). When present in adults these appear to have been present for long periods of time, and have probably developed on an anoxic basis, the anoxia having occurred either at birth or in early life Because of the fact, however, that convulsions may also cause severe hypoxia, there are certain observers who feel that previous convulsions may possibly account for the changes observed, rather than alterations at or immediately following birth (43).

The close relationship between certain forms of psychomotor epilepsy and a psychotic syndrome more or less identical with schizophrenia has recently been stressed (44). In all cases described there was electroencephalographic evidence of disturbance of function in the temporal lobes and deeper structures It was suggested that the patients of this group be classified as having a schizophrenic reaction associated with temporolimbic system dysfunction. A current review of the medical treatment of epilepsy by Merritt stresses not only the standard and newer anticonvulsant drugs but also removal of organic or psychological factors in the seizures together with physical and mental hygiene (45)

Unusual manifestations of epilepsy.—Inappropriate or unmotivated laughter as an epileptic manifestation has been of recent interest. This may be a prominent part of focal seizures, or may be associated with various other epileptic symptoms Daly & Mulder, referring to the syndrome as "gelastic epilepsy," suggest that the laughter may be a manifestation of discharge in the temporal region (46), Druckman & Chao postulate a hypothalamic origin (47); Weil, Nosik & Demmy believe the seizures are secondary to disturbances around the third ventricle and diencephalon, with projection to the temporal lobe (48). Wood, Svien & Daly, in discussing abnormal or involuntary laughter, not in all cases definitely epileptic, state that such laughter may result from lesions ranging from the limbic system at the cortical level through the hypothalamic centers to the bulbar motor system (49).

It is well known that epileptic seizures may be precipitated by sensory phenomena of various types Stevens (50) and Bingel (51) have described attacks brought on by reading. After either brief or prolonged reading the

preceded by an increase in urinary aldosterone and retention of sodium (62). This is followed by sequestration of potassium, and both the serum and urinary potassium levels fall abruptly. As the attack subsides there is diuresis of sodium, increase in urinary potassium, and the urinary aldosterone returns to normal. They suggest that the common denominator is excessive intracellular sodium and have been able to prevent attacks by decreasing the sodium intake.

Hereditary episodic adynamia.—Gamstorp in Lund (63) and later Kaplan and his colleagues in Paris (64) have described a syndrome similar to familial periodic paralysis except for the presence of hyperkalemia during attacks. The episodes are brief in duration and usually come on during a period of rest after activity; they are prevented or mitigated by movement. They may be provoked by the administration of potassium. The condition is inherited as an autosomal dominant, is usually evident before the age of five, and improves with advancing age.

Serum aldolase in myopathies.—Evans & Baker report gross elevation of serum aldolase in 13 patients with pseudohypertrophic muscular dystrophy, with a moderate elevation also found in other types of muscular dystrophy and polymyositis (65). Normal levels were found in patients with chronic neurogenic muscular atrophy and amyotonia congenita

Narcolepsy

The fundamental manifestation of the narcolepsy syndrome is a disturbance of the sleep cycle, usually with persistent drowiness and periods of uncontrollable sleep (66). In addition, there may also be cataplexy, fugue-like episodes, sleep or relaxation paralysis, hypnagogic hallucinations, and other abnormalities of behavior (67). Diagnosis is important, because the analeptic drugs are highly effective in most cases, but the disorder is often unrecognized because final diagnosis rests primarily on the history. Electroencephalograms may reveal frequent episodes of drowsiness, but when recordings are made during the alert state there are no significant abnormalities (68). Ganado expresses the belief that evidence is strongly suggestive that the narcolepsy syndrome is a nonepileptic disturbance of subcortical origin. It appears to be a state of depression of the arousal system, possibly from a neurohumoral deficiency

Cerebellar Syndromes

Acute cerebellar ataxia is most prevalent in children under 4 years of age (69, 70). The onset is usually abrupt, often after a well-defined latent period following a nonspecific respiratory illness. The syndrome is usually self-limited, without residua or recurrences The etiology is undetermined, but clinical facts tend to support the theory of a secondary invading viral infection.

In all patients developing alcoholic cerebellar degeneration there is a background of protracted and excessive drinking and of malnutrition (71).

functions of the reticular activating system are its interconnections with the spinal cord, cerebral cortex, basal ganglia, cerebellum, and vestibular nuclei, and its response to humoral excitation.

Coextensive within the reticular activating system are systems which appear to exert influences which are oriented rostrally and others that are directed caudally. Principal among the influences directed cephalically is that mediated by a diffusely projecting system of neurons which subserves arousal, sustained wakefulness, and all the mental attributes of conscious awareness. Caudally oriented mechanisms include those which modulate muscle tone and movement, control sensory inputs to the nervous system, and mediate processes of visceral regulation. Interference with cephalically directed influences results in mental disturbances, coma, and the anesthetic state. Defects in caudally directed activity induce spasticity, tremor, and disturbances in motion as well as faulty perceptive phenomena. Evidence indicates, however, that the several activities are so interdependent as to be inseparable, since stimulation never elicits changes in one area of reticular function without inducing related changes in all others The reticular activating system, therefore, must be considered the great integrating mechanism of the brain without which unity of response to complex environmental stimuli is impossible. Investigation of its functions can be expected to extend knowledge concerning the intricacies of normal behavior Doubtless, in its dysfunction will be found the seeds of many nervous and mental disorders that currently plague man's understanding.

Muscular and Neuromuscular Disorders

In an attempt to clarify and define the fundamental histological alterations in muscle in disease states, four independent investigators, Greenfield, Shy, Alvord, and Berg, made individual studies of a large number of biopsy specimens (59) They were able to describe and illustrate the major varieties of pathological change in diseased muscle, and to correlate the various combinations of such change with clinical observations Walton, in a study of 17 cases which were diagnosed as amyotonia congenita in infancy, found that 8 recovered completely between the ages of 5 and 15 years, while 9 improved to some extent but showed evidence of persisting muscular disability throughout life (60). He entitles this syndrome "benign congenital hypotonia," "with complete recovery" or "with incomplete recovery." It is important to stress that not all cases with a clinical picture of amyotonia congenita have a gloomy prognosis Shy & Magee have described a new type of nonprogressive hereditary myopathy (61). The onset is early in life, the weakness is proximal, and there is delay in walking, but when the patients do learn to walk their disability remains stationary. The histological alterations consist of the presence of aberrant fibrillary bundles found in the center of almost every muscle bundle.

Intermittent aldosteronism in familial periodic paralysis.—Conn and his associates have demonstrated that attacks of familial periodic paralysis are

epithelioma of the base of the tongue. He died 10 months later and extensive pathological alterations of the cervical portion of the spinal cord were observed. The other developed a spastic paraparesis four and a half months after receiving 8000 air roentgens for a carcinoma of the larynx within a period of 38 days. She was alive, but with residuals, 39 months later. The clinical picture of postirradiation damage to the spinal cord is that of a progressive myelopathy, usually with onset after a latent period. Factors such as field size, target distance, tissue dose, filtration, and duration of treatment obviously influence the development and course of the syndrome. The damage to the nervous system seems to be a secondary effect of vascular degeneration.

Lipide composition of cerebrospinal fluid—Tourtellotte *et al.* have analyzed the lipide content of the cerebrospinal fluid in normal individuals, utilizing ultramicrochemical procedures (77). Their data confirm reports that normal cerebrospinal fluid contains such lipides as cholesterol, cholesterol esters, and phospholipides, but they were also able to demonstrate for the first time the presence of cephalins, lecithins, sphingomyelins, cerebrosides, and neutral fat in normal fluids

Urea for reduction of increased intracranial pressure—Experience both with experimental animals and human patients shows that urea is an effective and safe agent for the reduction of increased intracranial and intraocular pressure (78) It appears to be superior to any agent currently used for this, and is not as apt to be followed by a secondary rise in pressure It has been used in intracranial and ophthalmological surgery, in the management of postoperative cerebral edema and craniocerebral trauma, and in the successful treatment of so-called pseudotumor cerebri.

The vertebrate visual-system—Polyak, in a posthumous publication edited by Kluver, completely summarized the experimental, anatomical, clinical, and pathological investigations of the visual pathways and centers of vertebrates (79) Although the emphasis is anatomical and histological, much new and important material on the biology and pathology of the vertebrate visual system is included, and much important clinical material is incorporated. The importance of the visual system to the entire organism, as well as to the development of various animal forms and particularly man himself, is stressed

The clinical symptoms evolve rapidly, the maximum deficit being attained in a matter of weeks or months, with no change thereafter. Pathologically there is a primary cortical cerebellar degeneration, with discrete localization to the anterior and superior parts of the vermis and hemispheres and the flocculonodular lobe. Victor, Adams & Mancall suggest that although there appears to be a close relationship between alcoholism and cerebellar degeneration, the important etiologic factor may be malnutrition rather than the direct effects of alcohol.

Cerebellar degeneration after diphenylhydantoin administration—The major symptoms of acute diphenylhydantoin (Dilantin) intoxication are ataxia, nystagmus, and slurred speech. These effects are usually reversible upon withdrawal of the drug. Utterback and his associates, in 1957, reported that experimental animals will develop severe loss of Purkinje cells, damage to granule cells, and cystic gliosis of the cerebellar white matter after daily administration of diphenylhydantoin (72). Hofmann has reported similar changes, with virtual disappearance of Purkinje cells, in a patient who received 20 to 30 mg. per kg. daily, both intravenously and intramuscularly, for almost two weeks (73).

MISCELLANEOUS

Water intoxication—Water intoxication in man gives rise primarily to neurological signs and symptoms, with agitated delirium, convulsions, increased cerebrospinal fluid pressure, and hyperreflexia. It is usually a complication in the management of patients with posttraumatic oliguria, renal disease, endocrine disease, or chronic electrolyte depletion, but Swanson & Iseri have reported two cases of self-induction (74). In one there appeared to be increased susceptibility to water intoxication due to electrolyte depletion following vomiting, and in the other transient overhydration occurred secondary to inability to establish an adequate diuresis. The serum sodium concentrations were abnormally low, and the symptoms and signs subsided and sodium concentrations returned to normal after profuse diuresis and treatment with hypertonic sodium chloride. Dodge, Crawford & Probst studied experimental water intoxication in anesthetized rabbits (75). During the induction of hydration, serum osmolality and the concentrations of sodium, chloride, and potassium fall, and the volumes of the intracellular, extracellular, and plasma spaces are expanded, during recovery the volume of the intracellular space shrinks rapidly, irrespective of changes in the extracellular space or plasma volume. These observations suggest that change in osmolality with intracellular edema of the brain rather than hyponatremia or hypochloremia is the chief determinant of the disturbed brain function in water intoxication.

Postirradiation myelopathy—Itabashi and his associates have reported two cases of cervical myelopathy following radiation therapy (76). One patient noted the onset of neurological symptoms 15 months after he had received 10,484 air roentgens within a period of 27 days, directed at a lympho-

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PSYCHIATRY[1]

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THE CHANGING SCOPE OF PSYCHIATRY

One medical dictionary defines psychiatry as the recognition and treatment of diseases of the mind. A psychiatrist, according to this frame of reference, is a medical specialist in diseases of the mind (1). Classical definitions notwithstanding, in American psychiatry the trend has been to devote increasing attention and effort to the problems of life stress and to the treatment and prevention of neurotic disorders [Whitehorn (2)] Indeed, a logical extension of such a trend in the future would result in a redefinition of psychiatry as the study of human behavior, and the psychiatrist would become the medical specialist whose work was to understand and modify human behavior. Today we are feeling some of the reverberations of the trend. Already, as Smith (3) comments. "The role of psychiatry in medicine demonstrates the dissociative forces within a profession and the range of differences tolerated. Divisive forces include technical skills, conceptual systems, scientific orientation, historical background, and problems of confidentiality. Integrative forces are the professional politics of psychiatry and medicine, changing concepts in medicine, high social rewards to physicians and, most important, the continuing identification provided by shared early medical training. The result is the conflict-filled, role-reciprocal of psychiatrist-physician."It appears to this reviewer that the trend has many interesting implications for the future. Will multifarious interests dilute the psychiatrist's role with possible resultant loss of identity, or will it, by broadening psychiatry's base—including training—make psychiatry a more effective specialty? The next decade, as suggested by the current developments reviewed, will offer some of the answers.

The major subtitles and chapter headings of the standard annual surveys in psychiatry (4, 5, 6) give indication of the broadening interests and practices currently accepted to be closely related to or encompassed by the field of psychiatry. These include:

- Administrative Psychiatry
- Alcoholism and Geriatrics
- Child Psychiatry
- Clinical Neurology
- Clinical Psychiatry
- Clinical Psychology
- Endocrinology and Biochemistry
- Electroencephalography
- Epilepsy
- Experimental Psychiatry
- Family Care

[1] The survey of the literature pertaining to this review was completed in July, 1958.

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authority have, to a great extent, given way to the establishment of facts by the application of scientific methods to the complex problems of psychiatry, though to meet therapeutic obligation empiricism is still heavily relied upon Gantt (11), in his brief comment on objectivity in psychiatry, outlines the criteria for a scientific discipline: "(*a*) The items should be clearly defined and recognizable by separate, independent workers. (*b*) They should be obtainable by independent workers when the same situation is repeated (*c*) Given the same factors, recognizable by different investigators, they should lead us to predict results and happenings." The fact that an experiment once performed, because it deals with nonrepeatable time, can never be exactly duplicated should not deter us from pursuing scientific method in psychiatric research. Nor should the two common and conflicting shibboleths raised against psychiatric research deter its use, namely, on the one hand, that psychiatry would not err if the scientific method were followed rigorously and, on the other, it is impossible for psychiatry to use the scientific method in studying the complex vagaries of mental life.

Through 1957–58 the chipping away at the multifaceted frontiers of behavior has continued, though nature has been slow to relinquish its secrets. This year's refinements of older concepts and acquisition of data have been slow but steady and without revolutionary discovery. For purposes of convenience the assessment of a few of the representative contributions and developments in the field will be discussed under the headings of three different approaches the organic, the psychologic and the sociologic. It is obvious that no clear-cut boundaries exist, particularly in most clinical practice and in much research, chiefly of the multidisciplinary variety which has a combined approach as its basis. Thus, it is by the reviewer's prerogative rather than necessarily by the original author's intent that a piece of work will be found in one rather than another of the categories

ORGANIC APPROACH

Research

Historically and, for the most part, today, the organic approaches in psychiatry are associated with the psychotic reactions Research has, by slow, deliberate plodding, succeeded in obtaining molecular data, though as yet unrelated to a satisfactory theoretical framework

Genetic level—Rainer & Kallman (12), conforming to the trend of the times, have reformulated the essential contributions which have been made by genetics to an integrated conception of psychiatric medicine. They give special consideration to the role of genetics, in theory as well as in practice, at the epidemiologic, psychodynamic, physiologic, and molecular levels.

Physico-chemical level.—Behavioral reactions associated with alterations of the structure or function of the central nervous system, or both, have long been known. The toxic reactions, exogenous or endogenous, are one example Depending upon how far back or in which directions one wishes to push the etiological links, one can state that the chemical agent is a "cause"

Forensic Psychiatry
Heredity and Eugenics
Industrial Psychiatry
Mental Health in Education
Military Psychiatry
Neuropathology
Outpatient Psychiatry
Physiological Treatment
Psychiatric Education
Psychiatric Nursing
Psychiatric Social Work
Psychoanalysis
Psychodynamics and Psychopathology
Psychophysiology
Psychosocial Studies
Psychosomatic Medicine
Psychosurgery
Psychotherapy
Rehabilitation & Occupational Therapy

The above subdivisions point to some of the definite problems to be dealt with, e g., the enormous mental hospital load, alcoholism, crime, "psychosomatic" disease, and plain unhappiness, as well as to the scope of psychiatrist's operational fields

In view of these developments in psychiatry it is not surprising that in the effort to gain depth, investigators and practitioners specialize further in ever smaller sectors. There results a multiplicity of diverse viewpoints on causality, pathogenesis, and therapy of disordered behavior. In 1956 Grinker (7) published the results of our interdisciplinary conferences which presage growing concerted efforts toward unification through discovery of concepts of human behavior applicable to all "systems," which he classifies as biological, psychological, and social Kruse (8), in considering the different trends, found it convenient to classify the current schools of thought into four major categories. (*a*) organic, (*b*) experimental psychological, (*c*) psychodynamic, and (*d*) psychosocial Each approach has its divisions and subdivisions, and each of the four groups has its own distinctive methodology, vocabulary, and doctrine Kruse's volume is an outgrowth of the efforts of 48 participating specialists to unite the four separate divisions into a joint enterprise a multidisciplinary approach to mental disorders Similar efforts to bring its concepts abreast of its data may be seen in other behavioral sciences, particularly in biology [Gerard (9)] The division into discrete, although theoretically related, systems is reflected by a deep split in the practice of psychiatry in the United States Redlich (10) refers to the two practice groups in psychiatry as the analytic-psychological (A & P group) and the directive-organic (D & O group) He discusses in greater detail the basis of this division and the reasons for the existence of a strong A & P group in relation to the culture of our country, and expresses his hope that in due time the various psychiatric schools and factions will mature and evolve into one scientific psychiatry

In line with the trend of the past two decades, the therapeutic mood continues eager and to some degree has usurped the enthusiasm and industry available for the hard tasks of reaching a more fundamental understanding [Whitehorn (2)] Notwithstanding, research in psychiatry is continuing its upward path Superstition, intuitive revelation, and appeal to

authority have, to a great extent, given way to the establishment of facts by the application of scientific methods to the complex problems of psychiatry, though to meet therapeutic obligation empiricism is still heavily relied upon. Gantt (11), in his brief comment on objectivity in psychiatry, outlines the criteria for a scientific discipline: "(*a*) The items should be clearly defined and recognizable by separate, independent workers (*b*) They should be obtainable by independent workers when the same situation is repeated. (*c*) Given the same factors, recognizable by different investigators, they should lead us to predict results and happenings." The fact that an experiment once performed, because it deals with nonrepeatable time, can never be exactly duplicated should not deter us from pursuing scientific method in psychiatric research. Nor should the two common and conflicting shibboleths raised against psychiatric research deter its use; namely, on the one hand, that psychiatry would not err if the scientific method were followed rigorously and, on the other, it is impossible for psychiatry to use the scientific method in studying the complex vagaries of mental life.

Through 1957–58 the chipping away at the multifaceted frontiers of behavior has continued, though nature has been slow to relinquish its secrets This year's refinements of older concepts and acquisition of data have been slow but steady and without revolutionary discovery. For purposes of convenience the assessment of a few of the representative contributions and developments in the field will be discussed under the headings of three different approaches. the organic, the psychologic and the sociologic It is obvious that no clear-cut boundaries exist, particularly in most clinical practice and in much research, chiefly of the multidisciplinary variety which has a combined approach as its basis Thus, it is by the reviewer's prerogative rather than necessarily by the original author's intent that a piece of work will be found in one rather than another of the categories

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logical soundness, and organized efforts such as the 1956 conference on the evaluation of pharmacotherapy in mental illness which was sponsored by the American Psychiatric Association and the National Institute of Mental Health, the confusion would approach chaotic proportions. Hollister's (18) brief and conservative comments on the present status of tranquilizing drugs supplement Wikler to bring us up to date.

Two studies on the effects of tranquilizing drugs which have superficially different results are particularly thought-provoking when examined together. The first is a carefully conceived and designed three-phase experiment to appraise the clinical effect of four drugs (reserpine, methylphenidate hydrochloride, trihexyphenidyl, and amobarbital) upon a hospitalized group of patients diagnosed as having chronic schizophrenic reactions [Rashkis & Smarr (19)]. In the first phase, in which the drugs to be tested were not administered, the patients were transferred to a research ward for a 28-week period during which they were evaluated on specially designed rating scales to establish a base line against which changes associated with medication were to be measured during phases two and three. During phase one, the "study and waiting" period of 28 weeks, it was found that 39 of the 48 patients showed measurable improvement in behavior. This change the authors termed the "milieu effect." During phase two, a 16-week period of drug administration, no significant effect on the clinical status was noted with reserpine or the other drugs, or with any combination thereof. Improvement during the drug phase thus was not attributable to drugs, but rather it was strikingly inversely related to the improvement during the predrug phase. The investigation of Savage & Day (20) was directed toward gaining more understanding of the psychodynamics of behavioral changes associated with reserpine by the intensive study of a few patients during a six-month period. The four patients studied had been in the same therapeutic milieu with high nurse-patient ratio, intensive psychotherapy, and all efforts to provide specialized and individual care for two years prior to the start of the study. The authors observed that with 5 mg daily of reserpine intramuscularly (*a*) the patient's and concomitantly the staff's anxieties appeared to decrease, (*b*) the patients were more friendly and outgoing, less preoccupied, and showed greater self-control and social conformity; (*c*) depression was not uncommon; (*d*) the patient's thinking became less dominated by primary process, secondary process came into play, delusional material became less prominent in waking life and made its appearance in the dream; (*e*) psychotherapy was a more agreeable collaboration, but one in which sensitive topics were still avoided; and (*f*) these effects were reversible when the drug was discontinued, or when unfavorable environmental stresses were present. The authors postulate that these effects of reserpine arise from the strengthening of the perceptual and repressive barriers of the ego. Upon examination of the necessarily sketchy historical material, this reviewer notes that three (A, B, and C) of the four patients responded to medication as summarized above, but the fourth (D) "was made worse." Patients A, B, and C who had been previously hospitalized

of a portion of the behavioral change, or often responsible for the inability to respond with socially acceptable and self-beneficial behavior.

In the past several years the discovery of chemical agents which, in minute amounts, are involved in the production of gross behavioral change has given credence to former speculations that chemical dysfunction plays a role in the etiology of disordered behavior. Concomitantly, the knowledge of the biochemistry of the nervous system (13) has grown steadily. Endogenous concentrations of chemicals to 1 gamma per kilogram of body weight are well within the range of physiological limits, and interference with neurometabolic processes by lesser traces of chemicals are thoroughly substantiated. Based on data stemming from such knowledge, four current chemical theories of psychosis are briefly described by Rinkel & Solomon (14). However, the most comprehensive survey of this cluttered field was done by Wikler (15) who has painstakingly reviewed the effects of many drugs, including the tranquilizers, on human behavior and has presented the current theories and mechanisms of the drug actions.

Investigations with lysergic acid diethylamide (LSD), the prototype of many currently used psychotomimetic drugs, continue. Notwithstanding the fact that there has been little clarification of the nature of the central action of this drug, two preliminary studies shed further light on the essential character of the behavioral changes associated with LSD-25. In one study, using minimal dosage in young men without apparent emotional problems, it was shown that physiological changes in general were absent with doses below 20 gamma, but cycles of rapid and profound shifts in affect were induced at 7 gamma, and were not rigorously differentiable from "toxic organic changes occurring before clouding of consciousness" [Greiner and co-workers (16)]. In the other experiment, using dosages of 25 to 200 gamma, it was found that "for both" normals and schizophrenics there is a significant increase in the perceived size of one's own body and its parts, and no significant change in the perceived size of external objects [Liebert *et al.* (17)]. The authors interpreted their findings in terms of the assumption that LSD operates as a "primitivizing agent," which is assumed to lessen the definiteness of the boundary of the body in relation to the surroundings

Treatment

Essentially, the physico-chemical therapies in psychiatry have been empirically derived. A division of such treatments into (*a*) tranquilizing drugs and (*b*) other somatic therapies (principally electroconconvulsive, carbon dioxide, insulin, and psychosurgery) would reflect the current tide.

Tranquilizers.—Although tranquilizing drugs are now second only to the broad spectrum antibiotics in dollar sales and number of prescriptions written, most of the voluminous clinical literature regarding them consists of reports of trials and impressions. With the introduction of ever-increasing numbers of tranquilizers and combinations of tranquilizing drugs the flurry of clinical appraisals which is now in its fifth year is bound to continue. Were it not for the interspersed studies which at least strive for methodo-

of quality, is very active with much repetition and often without the addition of anything new. Rampant theoretical speculations have brought some refinements and expansions of concepts, whose worth can be evaluated only in the future. The exciting early research on sensory deprivation has been rather quiescent with respect to publications this year. A bright spot is the trend toward increased research with rigorous design and method aimed at developing and testing hypotheses.

Theory

Psychoanalysis.—Psychoanalytic contributions to the understanding of the psychology of human development and behavior continue at a rapid rate and are reviewed in detail elsewhere, although there was regrettable delay of about 4 years from the time of survey to that of publication [Frosch & Ross (28)]. Hidden in this year's literature under the title of "Comment" is an illuminating, informal exchange of views on psychic energy and psychoanalysis between two students of human behavior, psychoanalyst Colby and physiologist Lashley (29). Linn (30) defines several areas of psychosomatic research to which psychoanalysis has contributed and he illustrates the way in which psychoanalytic knowledge has modified concepts and management in psychosomatic medicine. With the exception of its use as a method for exploring unconscious mental processes, the article deals with the theoretical contributions, namely, (*a*) unconscious mental processes as experimental variables; (*b*) psychological relationships between the experimenter and experimental subject; (*c*) problems of perception and defense, and (*d*) the concept that early infantile experiences exert lasting and all-pervasive influences on subsequent emotional developments.

The most comprehensive study which attempts to integrate psychoanalytic theory with physiologic research is from the Institute for Somatic and Psychiatric Research and Training of the Michael Reese Hospital. The first of their series of several papers which began in 1956 is entitled "A Theoretical and Experimental Approach to the Problem of Anxiety" and gives the general background of the research as well as outlines the over-all experimental design, the choice of subjects, and the variables studied [Grinker *et al.* (31)]. To that series of publications the Michael Reese team has added several during the past year, most of which can be grouped under the following variables: (*a*) affects, (*b*) perception and decision, (*c*) physiological measures, and (*d*) hormonal measures.

In a paper on the significance of pre-experimental studies in the psychosomatic laboratory during which psychological and physiological observations were made, it was shown that the process of acclimatization to a laboratory setting may constitute a special stress for the experimental subject and that such an initial day cannot be considered a psychologically neutral condition for the assessment of a basal or resting state a priori [Sabshin *et al.* (32)]. It was pointed out that anxiety was relatively high on the pre-experimental day compared to the subsequent three experimental days. In addition, plasma hydrocortisone showed a striking reversal of

about 3, 1, and 0 or 2 years, respectively (data concerning patient C's previous hospitalization are not clearly given) before entering the therapeutic milieu of the research hospital, rapidly regressed upon admission and continued their regressive patterns. Patient D, on the other hand, had been institutionalized for 15 years and had finally ended on the most regressed ward in the state hospital. Upon transfer to the research hospital she showed no further regression, and, indeed, is described as having qualities of attractiveness, considerable appeal, and was able to appear openly demonstrative and affectionate to the staff whose "favorite patient she was." It appears that here, as in the case of the patients of Rashkis & Smarr, there is an inverse relationship between predrug change ("milieu effect") and the changes with drugs. If so, why? Rashkis & Smarr (19) raise the question of whether patients who benefit from milieu change will continue to benefit if the milieu is consistently modified rather than from drugs being introduced in the hope that the patient will thus be "made just a little better" or "carried over the hump." Perhaps their question may be altered to read as follows. During the course of milieu therapy of a psychotic patient when is it optimal to use adjunctively further measures such as medication aimed at strengthening the protective stimulus barrier of the ego to allow him to regain, if only temporarily, some of his discriminatory powers?

Other somatic therapies.—Insulin treatment flourished for nearly 20 years, but its hazards, expense, and the failure of its empiricism to withstand critical inspection have all but resulted in its demise in 1958 [Bourne (21)]. Psychosurgery, which reached its peak about 10 years ago, is nearly obliterated and only its staunchest advocates see any prospects for its continued use as a therapy in psychiatry [Freeman (22)] The indications for electroconvulsive treatment, which are under persistent re-evaluation, are clear for at least symptomatic alleviation of a certain form of severe depression. Carbon dioxide treatment, carried forward by a relatively few dedicated adherents, seems to be generally on the wane.

There have been numerous hypotheses, physiological and psychological, as to the mode of action of electroconvulsive and carbon dioxide therapies. The prominent physiological theory of sympathetic reactivity at the hypothalamic level, expounded by Nelson & Gellhorn (23), had received clinical confirmation from Funkenstein, Moriarty (24), and others using the methacholine test as developed by Funkenstein *et al* (25) Two recent studies raise serious questions as to the reliability of the methacholine test, and therefore as to its validity as an indicator of either prognosis of electroconvulsive therapy or autonomic responsivity [Lotsof & Yobst (26) and Maas (27)]. In addition, one of the studies (27), though methodologically less sophisticated, suggests that when a drug is given the resultant effect will frequently be a function of the chemical, the patient, the examiner, and the interaction of the three

PSYCHOLOGIC APPROACH

Articles relating to material which could be included under the rubric of the psychologic approach are voluminous. Data collecting, of all degrees

responded with only a slightly greater increase in plasma hydrocortisone than the normal, but at the same time anxious subjects excreted far more hydroxycorticoids in the urine. Upon repetitive infusion of corticotropin, the plasma hydrocortisone level prior to each day's injection rose progressively in anxious subjects, but stayed constant in the controls.

It is of note that although the Michael Reese experimental program was derived primarily from a psychoanalytic theoretical orientation, the data obtained can fit comfortably within the framework of contemporary learning theory. Certainly, hypotheses applicable to the findings thus far presented by the Michael Reese group can be derived from a learning theory approach

Other theories.—Although it is indeed not necessary for a theory to be global in order to be useful, behavioral theories other than those closely related to the psychoanalytic have generally been rather limited in scope This tendency often greatly impairs their usefulness in the understanding of human development and behavior in a social setting and, thereby, their applicability to clinical work. It is nevertheless regrettable that even mention of most theories must be omitted

However, the reader's attention is called to Bowlby's (39) novel and delightful discussion of the application of ethological concepts to child development research. He also briefly reviews the main characteristics of this approach which deals with species-specific behavior patterns.

During this past year Wolpe (40) has made a concerted effort to extend a condition-response explanation to the etiology of human neuroses and to their treatment Wolpe's attempt to extend his theory, which allows for the prediction and control of animal behavior in limited settings, to neurotic behavior in humans, is convincing to a point, and Part I of his book which is devoted chiefly to this aspect is, indeed, a sophisticated contribution. Part II, entitled *Psychotherapy*, is a conglomeration of empirically derived procedures loosely bound under the concept of the "reciprocal inhibition principle," replete with references to analogous procedures on experimental animals Though dignified with other names, the procedures are of the nature of supporting, advising, suggesting, directing, exhorting, and systematic training, with the criteria for cure and improvement being primarily the symptomatic status and, secondarily, the score on the Willoughby Personality Schedule. Wolpe attributes the "50 per cent" measure of success by conventional methods of psychotherapy ("counseling to psychoanalysis") to the nonspecific reciprocal inhibition effects of interviewing and of the psychotherapeutic situation. With the addition of his special methods the figure rises to 90 per cent. The author wisely acknowledges, and most will agree, that in a matter like this, conviction cannot be founded on one man's experience.

Psychotherapy

While some presume that psychotherapy has reached the status of a separate scientific discipline, the fact that much more remains unknown than known about it has not been significantly altered in the past year.

diurnal pattern on the first day and urinary hydroxycorticoids, though not significantly higher than on experimental days, were elevated above normal values. Of methodological significance is the observation that both the inherent novelty and ambiguity of the experiment-laboratory situation and the idiosyncratic meanings given to it by the subject can constitute a psychological stress.

A paper on affective variables asserted that independent, trained observers were able to make highly reliable statements of observations differentiating anxiety, anger, and depression [Hamburg *et al.* (33)] These statements included not only the presence or absence of these emotions but also the extent to which each was experienced by the subject.

Two of the papers related to perception and decision [Korchin *et al.* (34, 35)]. It was found (34) that at moderate levels increased anxiety facilitates, whereas at higher levels a similar increase of anxiety disrupts performance based on perceptual functioning measured in terms of accuracy and speed of visual discrimination of objects differing in stimulus attributes. In another experimental situation which was designed to lead the subject to believe that his perception was inaccurate or distorted (35), the findings were that such stress produced emotional response. However, the normal subjects' responses were more specific and appropriate to the focal stresses, and in general more adaptive than patients' responses which were more related to the situation in general and less to the specific stress events. The experimental findings appear to confirm the hypotheses that the following factors are important in determining the stressfulness of a situation. (*a*) the relevance of the stress agent to frustration of the subject's needs; (*b*) the subject's ego strength and defenses, and (*c*) the relation between the stress condition and the larger psychosocial situation.

A paper on the physiological variables dealt with temporal heart-rate patterns in anxious subjects [Glickstein *et al.* (36)] It is interesting to find that by simply averaging heart rates of all subjects, no apparent experimental effect on the heart rate is shown. However, two subgroups were derived factorially, the clinically more, and clinically less anxious patients, respectively. The latter showed a relatively level heart rate over the entire day, with distinct rises in immediate response to threatening situations The former, more disturbed patients, showed a high initial level with an over-all lowering of heart rate from the beginning to the end of the experimental day without peaks related to specific events

Lastly, as to hormonal measures, two papers were published by the group [Persky *et al.* (37, 38)]. Changes in the plasma hydrocortisone level were linearly related to the degree of increase of any emotional arousal, whether anxiety, anger, depression, or any combination of these (37) The highest increases in hydrocortisone after a stressful interview occur when the subject experiences (*a*) a sharp increase in emotional distress; (*b*) a prolonged high level of emotional distress; or (*c*) thought implying profound threat, whether or not the immediate distress is very great Relative to the effect of intravenous corticotropin administration (38), it was found that anxious subjects

37 original patients none were considered psychotic and all were doing well In their 10-year follow-up study of the 19 patients on which adequate material was available, Horwitz and his co-workers concluded that the 12 of these who were originally considered at the New York Psychiatric Institue to be schizophrenic had 10-year adjustments consistent with the usual course of untreated schizophrenic patients The remaining seven, originally considered as nonschizophrenic at the Institute, followed a course similar to that which one would ordinarily expect in a 10-year survey of nonschizophrenic patients

Research.—Research on psychotherapy presents many difficulties, not the least of which is the possiblity that intrusion upon the confidentiality of the patient-therapist relationship will interfere with the maximal effectiveness of treatment. There is no question but that examination of the therapeutic process in action in itself alters the process in many ways Nevertheless, if valid knowledge is to be obtained, the multiple variables relating to psychotherapy must be systematically scrutinized.

Until recently most research has been focused on the patient, with some assessment of the kind of therapeutic climate provided by the therapist via the "technique" he uses. Gradually, as more work has been done on the therapist-patient interaction, it has become increasingly evident that the therapist himself must be thoroughly studied, too, if we are to understand treatment.

If an exploratory study on the biases of a total of 17 psychotherapists of three different orientations, Lakin & Lebovits (47), using a laboratory rather than a clinical situation, found it possible to classify into three categories the therapist's associations to a few scanty historical facts about a patient These were speculations about etiologic factors, diagnostic issues, and therapeutic issues Preliminary findings indicate that therapist orientation (predisposing sets or biases) selectively influenced the conceptualization of a patient when only minimal information is provided.

More elaborate and carefully conceived is the study of the psychotherapist's contribution to the treatment process by Strupp (48) His investigation "attempts to explore how the therapist structures the therapeutic problems (perceptions and evaluations), how these conceptualizations are related to what he proposes to do (treatment plans, goals, proposed procedures), and what he actually does (technique) " The aim was "to investigate these interrelationships as well as to explain possible differences among therapists in terms of systematic effects produced by their training, experience, and personalities " The procedure used was, again, a laboratory rather than a clinical situation. A sound movie of a 35-min initial interview in which Finesinger's technique of minimal activity was used, was interrupted for 30 sec at each of 28 predetermined points, giving the audience therapist an opportunity to indicate what he would do if he were the interviewer. Following the film, the therapists were requested to complete a comprehensive questionnaire relating to the film as well as one on biographical information Of the sample of 237 therapists, 134 were psychiatrists, includ-

Nevertheless, many thoughtful theoretical and methodological articles, particularly with reference to research, have appeared.

Concepts.—In papers dealing with psychoanalytic theory and psychotherapeutic methods, Szasz (41, 42) illuminates the importance of identifying clearly the distinctive features of the various diverse modes of psychotherapy. He proposes that "psychoanalysis" be used only to denote an expanding area of theory, and that "the different psychological operations be clearly designated by different expressions (e g., the primary model technique, therapy by example, etc.)" rather than grouped under psychoanalysis. Such operational redefinition in itself may be helpful in reducing the misunderstanding which results from the continuing side-by-side existence of conflicting opinions, using the same words, but derived from different methods of observation. It seems also likely that such clarification is a prerequisite to a better understanding of the therapeutic process.

However, regardless of the preciseness of definition of the method, psychotherapy remains an interpersonal phenomenon between participants in a social field. In scrutinizing the interpersonal relation between therapist and patient, Bromberg (43) encountered "the application of scientific technology which involves certain psychologic overtones of extratechnical nature operating within the therapist" whatever his postulates, premises, or theories of psychotherapy. This Bromberg names "therapeutic artfulness" and suggests it "as the most plausible way to explain successful therapy when conducted by workers who point to the most diverse scientific theories and formulations as a valid basis for their accomplishments." Grinker, in discussing Bromberg's theoretical paper, points out some of the significant variables for effectiveness in psychotherapy as including the patient, therapist, verbal and nonverbal communications between them, the life situation, and the inner and outer changes in the mental life and behavior of the patient.

In a masterful, clinically oriented presentation Will (44) summarizes his views regarding the psychotherapy of schizophrenia and certain conceptions upon which that treatment is based On these topics Will has prepared and appended an excellent annotated bibliography including related literature published during 1956 and the first half of 1957

Therapeutic outcome.—"Cure," "improvement," and "successful therapy" have been mentioned in this review What are the criteria? Snyder (45), in discussing studies of psychotherapeutic outcome, points out that criteria for the most part are quite subjective and judgments of outcome frequently consist of the therapist's impression. Only occasionally are the criteria more objective, and only recently have factor analytic studies, which show much promise, been used. In general, the more rigorous the criteria the less encouraging are the reported results For example, this year Horwitz and his co-workers (46) reported a follow-up study of patients with schizophrenic reactions treated by "direct analysis " They point out that in 1947 Rosen reported a therapeutic technique which he claimed resulted in recovery of all 37 patients treated. In 1952 Rosen reported that of 31 of the

combined. Convinced that "upgrading" of patients could be achieved by social manipulation within the hospital setting, Greenblatt and his co-workers (50) directed intensive efforts of the same general type to rehabilitation in the community. Their preliminary experiences show that such a program has had a noticeable reciprocal impact on the hospital structure with differential effects on the various traditional role groups Psychiatrists and social workers appear threatened by the new emphasis while nurses, and occupational and industrial therapists have enjoyed a reinforcement of their status.

Social treatment, as it is practiced in the United States today, had its rebirth within the past decade or so in England. In commenting upon the use of the mental hospital as a therapeutic instrument Cohen (51) briefly reviews the recent history of some of the interesting innovations which British psychiatrists have been carrying out in the general area of social psychiatry. He points to the changing atmosphere of the mental hospital from that of a restrictive custodial institution to one of a rehabilitation center to which patients come voluntarily for help. Cohen emphasizes that the open-door policy and giving the patients increasing responsibilities for the direction of their daily activities play important parts in the remarkable change in hospital atmosphere. Surrender of the key by the staff and the termination of dealing with problems by authoritarian measures such as seclusion, restraint, and transfer to a disturbed ward have resulted in different staff-patient attitudes In turn, problems are now resolved by changes in personal relations between patients and staff. Hurst (52) considers the problems raised by the unlocking of the chronic wards at Shenley Hospital in England. He points out that elopements occurred no more frequently than prior to unlocking the door. The principal difficulty occurred with "deteriorated, confused schizophrenics " He suggested that a well-developed program of occupational therapy established several months prior to opening would have probably reduced most of the problems He speculates further that "deteriorated schizophrenics" might never have reached that stage had they spent their hospital life on an open ward He postulates removal of all contacts with the outer world as the principal precipitant of their "deterioration." Rapoport & Rapoport (53) studied the social processes at Belmont Hospital, England. They point out how an experimental form of organization aimed at "democratizing" the authority system has evolved in the attempt to resolve the problem of avoiding coercive authority in patient-therapist relationships in a hospital setting where considerable centralization of authority is necessary for hospital administration alone The desirable features, as well as the hazards, of their model for authority are discussed and are compared with the model described by Stanton & Schwartz (54).

Probably the most intensive and extensive study and description of a therapeutic community in the United States is that by Wilmer (55) of a psychiatric ward at the U. S. Naval Hospital in Oakland, California Even though it was a locked admission ward where patients were kept no longer than ten days and the goal was primarily patient management, their ex-

ing 43 residents, and it was the responses of the group of 134 trained in medicine with which the paper primarily dealt. The analysis of the data and its statistical treatment appear sound. The more minute findings which are too numerous to list, are of interest and have potentially valuable implications for the practice of and training in psychotherapy. Two broadly defined groups of therapists appear to emerge from the investigation, though there were many subgroups which did not follow the pattern. Group I therapists appear to be more tolerant, humane, permissive, and democratic; while Group II therapists emerge as more directive, disciplinarian, moralistic, and harsh. Could it be that the aforementioned A & P and D & O practice groups (10) have at least some of their roots in the personality groupings I and II of Strupp?

SOCIOLOGIC APPROACH

Social Psychiatry

For nearly a century sociology has contributed its concepts and methods to the study of social organization and structure, and to the examination of the way the individual participates in his society. Within the past three decades there has been increasing recognition that social factors are involved in personality formation and in the etiology of psychopathologic conditions. More recent convergences of sociology and psychiatry have contributed to a shift of viewpoint in which the added dimension of the interpersonal factor allows consideration of psychopathologic states as types of deviant participation in social processes.

Scattered throughout the literature this past year are numerous contributions of psychiatrists, sociologists, anthropologists, and others to the still loosely bound body of knowledge which comprises social psychiatry. Rather than cite a few of the recent publications which are representative of current developments, the reviewer refers those readers who are interested in looking deeper into one of the most promising frontiers of medicine to a book edited by Leighton, Claussen & Wilson (49) which deals with a wide range of reciprocal contributions of psychiatry and sociology. Special attention is called to two chapters. The first is the chapter on orientation, in which an attempt is made to bridge conceptually the gulf between intrapsychic and interpersonal patterns The other is a chapter by Hinkle and Wolff in which the fact that man's relation to his social environment has a major influence upon his health is quantitatively highlighted.

The Therapeutic Community

Perhaps the most exciting development associated with the sociologic approach is the refocus on the concept of the milieu as a therapeutic agent. Incorporating concepts contributed by sociology are the social therapeutic clubs, halfway houses, day hospitals, night hospitals, and hospital therapeutic communities, all of which may be said to be examples of social psychiatry in action. Probably a greater number of such units has been established in this country during the past year than in the preceding eight years

combined. Convinced that "upgrading" of patients could be achieved by social manipulation within the hospital setting, Greenblatt and his co-workers (50) directed intensive efforts of the same general type to rehabilitation in the community. Their preliminary experiences show that such a program has had a noticeable reciprocal impact on the hospital structure with differential effects on the various traditional role groups. Psychiatrists and social workers appear threatened by the new emphasis while nurses, and occupational and industrial therapists have enjoyed a reinforcement of their status.

Social treatment, as it is practiced in the United States today, had its rebirth within the past decade or so in England. In commenting upon the use of the mental hospital as a therapeutic instrument Cohen (51) briefly reviews the recent history of some of the interesting innovations which British psychiatrists have been carrying out in the general area of social psychiatry. He points to the changing atmosphere of the mental hospital from that of a restrictive custodial institution to one of a rehabilitation center to which patients come voluntarily for help. Cohen emphasizes that the open-door policy and giving the patients increasing responsibilities for the direction of their daily activities play important parts in the remarkable change in hospital atmosphere. Surrender of the key by the staff and the termination of dealing with problems by authoritarian measures such as seclusion, restraint, and transfer to a disturbed ward have resulted in different staff-patient attitudes. In turn, problems are now resolved by changes in personal relations between patients and staff. Hurst (52) considers the problems raised by the unlocking of the chronic wards at Shenley Hospital in England. He points out that elopements occurred no more frequently than prior to unlocking the door The principal difficulty occurred with "deteriorated, confused schizophrenics " He suggested that a well-developed program of occupational therapy established several months prior to opening would have probably reduced most of the problems. He speculates further that "deteriorated schizophrenics" might never have reached that stage had they spent their hospital life on an open ward. He postulates removal of all contacts with the outer world as the principal precipitant of their "deterioration " Rapoport & Rapoport (53) studied the social processes at Belmont Hospital, England They point out how an experimental form of organization aimed at "democratizing" the authority system has evolved in the attempt to resolve the problem of avoiding coercive authority in patient-therapist relationships in a hospital setting where considerable centralization of authority is necessary for hospital administration alone The desirable features, as well as the hazards, of their model for authority are discussed and are compared with the model described by Stanton & Schwartz (54).

Probably the most intensive and extensive study and description of a therapeutic community in the United States is that by Wilmer (55) of a psychiatric ward at the U. S. Naval Hospital in Oakland, California. Even though it was a locked admission ward where patients were kept no longer than ten days and the goal was primarily patient management, their ex-

perience serves as a most illuminating example of problems faced, methods of meeting them, and results obtained through the establishment of therapeutic community concepts.

Young (56) reports 16 months' experience with an open-door therapeutic community in a 30-bed psychiatric receiving service of a suburban general hospital. Data are available on 1624 patients, nearly all of whom were hospitalized by court order and could not be screened or refused admission All patients regardless of sex or severity of illness were treated on the same ward by staff, the majority of whom, with the exception of psychiatrists and social workers, had little previous psychiatric experience. The basic philosophy of the unit is based on two principles. The first is that of the unrestricted communication between patients and staff which implies mutual courtesy, consideration, and a willingness to understand. The second is that of expectation that the patient will utilize maximally the healthy aspects of his personality. In this setting only liquor, razor blades, and personal medications are excluded. Such items as scissors, mirrors, and nail files are considered necessary and useful. The chief therapeutic instrument is the ward group composed of both patients and staff which meets daily. A number of special activities, such as arts and crafts, gardening, housekeeping, and use of the kitchen are encouraged In addition, other standard forms of psychiatric therapy are available, but their use seems rarely indicated. Locks are used only in extreme emergency situations when "all else fails." So far, there have been only four of the 1624 who probably could not have been treated on the ward with an open door. Of the total patients admitted 68 per cent have returned to the community after an average stay of seven days, while about 28 per cent have been referred to other hospitals voluntarily or by commitment, the majority of these being chronic psychotics or chronic alcoholics. In general, hypomanic and depressive patients were the most difficult to treat in the setting described while schizophrenics, alcoholics, and character disorders have responded well. The reviewer regrets that he must omit many further interesting details of this pioneering effort

Wilmer (57) points out that "the basic departure of the therapeutic community concept from traditionally established concepts of the mental hospital is the emphasis that it places upon socio-environmental factors in the patient's hospital experience. In the hospital which operates as a therapeutic community, socialization and the sense of belonging take their place along with psychotherapy. The traditional order of hierarchy is reversed, and the hospital is regarded as the patient's world rather than the doctor's domain, thus, the traditional staff attitudes and staff-patient relationships are considerably altered. So also are the procedures employed: self-control, dignity, and trust supplant excessive imposed controls, restrictions, regimentation, and tradition-bound rituals " Since hospitals which practice the therapeutic community concept vary in structure, process, and pattern, a method of discriminating between similarities and dissimilarities is necessary in order to compare them scientifically and evaluate results. One basis for making such an identification as outlined by Wilmer (57), includes 32 points of refer-

ence subsumed under headings of facilities, patient sample, staff, therapy, research and evaluation, and legal status of patients

Evaluation of the efficacy of therapeutic communities will undoubtedly prove to be a difficult task, one in which such studies as Hastings' (58) follow-up results in psychiatric illness may well become a valuable model. The reviewer thinks that therapeutic community care will be found to be of significantly greater value than current standard hospital care. This opinion is reinforced by a brief experience with an open therapeutic community ward in Stanford University's general hospital The therapeutic community concept will make a deep imprint in the future practice of medicine.

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SPECIAL THERAPEUTICS (TRANSFUSIONS)[1]

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The purpose of this presentation is to review the more important experimental and practical accomplishments in the field of transfusion therapy during the past year. Progress in the fields of blood preservation and transfusion therapy continues at a rapid pace. The most notable achievements have related to an improved understanding of transfusion reactions, modified and new indications for exchange therapy, and the effects of *in vitro* storage conditions on the *in vivo* survival of various blood constituents. Despite these advances, the misuse of blood transfusion therapy continues to be a major problem. The enormous impression in the minds of many physicians that the routine and rapid restoration of all blood components to "normal" with transfused blood is a therapeutic necessity comprises the basis for this problem.

Transfusion Incidence, Indiscretions, and Indications

A report made in this past year by the Project Advisory Committee of the Joint Blood Council estimated that approximately 5,000,000 units of blood were administered in 78 per cent of the hospitals in the United States during the previous year (1). No systematic pattern of blood collection was noted and the breakdown was as follows: Regional American Red Cross collection, 38 per cent; voluntary hospital collection, 36 per cent; commercial blood banks, 11 per cent; nonhospital community blood banks, 9.5 per cent; hospital-to-hospital transfer, 4 per cent; and paid donors, 2 per cent. Irrespective of the system used, blood procurement in peacetime is a major problem, and each system has some deficiencies. In the state of Connecticut the American Red Cross collects and distributes all blood, yet in the neighboring New York City area 42 per cent of the blood is obtained from paid donors, and the estimated consumer cost varies from $14.00 to $60.00 per unit (2). In some areas as much as 80 per cent of the blood is purchased (3). The rapid increase in blood consumption is attributable to a number of factors (4). Intricate and long cardiovascular surgical procedures may require from 10 to 20 units of blood per patient. New demands have been made through greater appreciation of the value of exchange transfusions in infants with erythroblastosis and various toxemias, and the recognition of new hemophilioid states. Increased hospital costs have encouraged many physicians to transfuse pernicious anemia and iron-deficient patients so as to shorten their period of hospitalization. The routine transfusion of

[1] The survey of the literature pertaining to this review was completed in July, 1958.

preoperative, obstetrical, and cancer-bearing patients with slight anemia imposes severe demands on the blood bank. This flagrant misuse of blood is called by Crosby (5) "the secretarial practice of medicine." In citing certain obstetrical routines, Crosby goes on to say, "when the patient flunks her hemoglobin test the stenographer types out a transfusion request." He also mentions some services where surgical patients receive 1 liter of blood the day prior to operation, and instances where patients with malignancies receive 1 unit of blood if the hematocrit is below 38 per cent and 2 units if below 32 per cent. The surgical practice of having blood on hand for routine operations also wastes blood. In England approximately 14 per cent of all blood collected is not used before its expiration date (4). Chown (6) is adamant in his feelings about the misuse of blood, believing that over 50 per cent of all transfusions are unnecessary and that most transfusions to women under 45 years of age are unnecessary. Probably less than 1 per cent of these are life-saving. Dripps (7), in a concise review of these problems, quotes the British Consulting Pathologist Committee as follows, "It appears unjustifiable to place any patient at a risk for one pint of blood." In one large medical center 45 per cent of the patients transfused received but a single unit (8) The misuse of blood has promulgated the philosophy among several authorities that a single physician in charge of the blood bank should have authority to disapprove individual transfusion requests (4, 9) The proper use of blood could save as many as 2,000,000 units of blood in the United States alone, and could prevent as many as 400 to 600 unnecessary deaths annually. This figure is based on the transfusion mortality of 1 per 5,000 (7), an incidence comparable to that of appendectomy.

What are the indications for transfusion? Crosby (5) has defined them as follows: (*a*) to improve the stability of the circulatory system when the blood volume has been reduced in such a way as to imperil the patient; and (*b*) to improve the oxygen-carrying capacity of the blood to prevent acute hypoxia or invalidism He points out that sedentary patients are comfortable with 10 gm. per cent of hemoglobin, since much of the normal hemoglobin mass is in reserve for exertion He questions the value of transfusion to "normal" before surgery, especially since no changes in the vital signs are demonstrable until the hemoglobin is 7 gm per cent or less Strict adherence to these criteria could appreciably reduce transfusion mortality. The lack of clear indications for the transfusion of patients has many serious medical legal implications (5, 10, 11).

Transfusion Reactions of the Immediate Type

The overall incidence of adverse acute reactions to transfusions probably is somewhere between 20 per cent and 40 per cent A recent small series showed an incidence of pyrogenic reactions alone to be 38 per cent (12). Others have found acute pyrogenic and allergic reaction rates as low as 5 6 per cent (13), 4 4 per cent (14), and 1.44 per cent (8). Most of the important types

of acute reactions are illustrated in Table I. Many of these are the result of improper laboratory technique, excessive transfusion, obscure immunologic catastrophe, and human error. Strict laboratory control of the entire operation under the direction of a competent physician is essential and invariably will help to reduce the incidence of serious mishaps (8, 15, 16, 17). In spite of extremely rigid rules in one series of 20,000 transfusions reported, 4 of the

TABLE I

IMMEDIATE ADVERSE REACTIONS TO BLOOD TRANSFUSIONS

Type of Reaction	Manifestations	Cause
"Simple" febrile	Fever, chills, headache, backache, etc	Donor protein, leukocytes or platelets plus recipient's natural or acquired protein, leukocyte or platelet antibody
Pyrogenic	Fever, chills, headache, backache, etc	Bacterial pyrogens
Toxic	Shock, hyperemia, fever, chills	Bacterial endotoxin
Allergic	Urticaria, asthma, joint pain, eosinophilia, etc	Hypersensitivity of recipient to donor "allergen"
Hemolytic	Chills, fever, hemoglobinemia, bleeding, hemoglobinuria, shock, anuria, death	Old blood Donor or recipient isoagglutinin or hemolysin
Leukopenic	Febrile reaction, leukopenia	Donor leukocyte antibody or leukolysin Allergic or pyrogenic reaction
Thrombocytopenic	Febrile reaction, bleeding	Donor platelet antibody Dilution thrombocytopenia Intravascular clotting
Cardiac	Signs and symptoms of acute pulmonary edema	Overtransfusion ? Citrate toxicity Hyperkalemia and hypocalcemia
Ac globulin deficiency	Bleeding, delayed coagulation	Dilution Intravascular clotting Fibrinolysis
Hypoprothrombinemia	Bleeding, impaired coagulation	Intravascular clotting Fibrinolysis
Hypofibrinogenemia	Bleeding, impaired coagulation	Intravascular clotting Fibrinolysis
Hypocalcemia	Tetany, cardiac arrythmia	? Citrate toxicity
Hyperkalemia	Cardiac arrythmia, convulsions, muscular twitchings, etc	Donor erythrocyte potassium loss
Air embolization	Dyspnea, sudden death	Air entry into vein

5 mismatched transfusion reactions encountered were caused by physician error (8). This is not an unusual occurrence and the possibility of such human error always must be weighed against the necessity for transfusion.

Many acute pyrogenic and allergic reactions to blood probably arise from individual idiosyncrasy to foreign protein, but there is increasing interest in recipient circulating isoantibody to the formed elements of the blood as a means of explaining these obscure reactions. This impression is supported by the high incidence of reactions in multiply-transfused recipients found in association with leukocyte agglutinins (18 to 23). Payne (21) has shown good correlation between the number of recipient transfusions and the incidence of positive leukoagglutination tests. There now is much to suggest that the immunologic structure of the leukocyte is extremely complex, and that the opportunity for isoimmunization is very high. Brittingham & Chaplin (22) transfused five patients who had had numerous previous transfusions and leukocyte agglutinins with leukocyte-depleted blood. Reactions were avoided in this group whereas they invariably reacted to untreated whole blood. These investigators have described simple methods for leukocyte and platelet removal from whole blood. Dausset *et al.* (23) were able to corroborate these results. Isoimmunization to platelets results in rapid removal of the transfused platelets from circulation (20), but probably does not produce major systemic reactions. On the other hand, the administration of donor blood with a high titer of platelet agglutinin will produce severe thrombocytopenia in a recipient (24). In this particular instance the donor had sarcoidosis, and the author advised against the use of such patients as donors. Erythrocyte isosensitization continues to be an important problem in spite of greatly improved laboratory techniques. Fudenberg & Allen (25) have demonstrated poor erythrocyte survival in certain recipients in spite of normal crossmatching with present techniques. It is their impression that present-day methods are incapable of detecting these incompatibilities They suggest giving group-compatible blood whenever possible to patients requiring multiple transfusions and not to rely solely on the crossmatch. Chown (26) condemns the practice of using universal donor blood without adequate crossmatching, and cites many examples of antiDuffy and antiKell reactions with shock and anuria when the crossmatching was inadequate He feels that many laboratories have not kept up with new immunohematologic knowledge The use of universal donor blood certainly is a serious potential hazard (26). In a recent panel discussion (3) it was noted that ABO sensitization is seen about five times as often as Rh sensitization, and that 97 per cent of ABO incompatibility reactions occur in group O recipients. Again the use of group specific rather than O, Rh negative blood even for emergencies was emphasized. In contrast, many of these problems do not concern certain racial groups such as in Thais, all of whom are Rh and Kell negative (27). Only one reaction was noted in more than 10,000 transfusions with only ABO typing, and that was owing to A_3 Severe erythrocyte hemolytic transfusion reactions fre-

quently are masked during surgical anesthesia (28), but may be detected rapidly by inspection of a centrifuged blood sample for the presence of free hemoglobin This report censures excessive use of blood in the operating room and emphasized that it should not be used unless the blood volume is low because of bleeding.

A satisfactory explanation for the remaining (nonspecific) transfusion reactions is lacking to date. Those attributed to bacterial pyrogens largely have been eliminated through the extensive use of disposable plastic recipient sets Other nonspecific protein reactions characterized by fever and leukopenia are thought by Nicolau (29) to result from antigenic stimulation of R.E. tissue with release of acetylcholine. He has reduplicated the hematological alterations characteristic of these reactions in man with intravenous injection of acetylcholine. Polak & Fiser-Herman (30) have found subnormal total protein levels (especially albumin) in many patients who reacted badly to blood They suggest that washed red cells should be given to these patients, and that this is preferable to antihistamine. These results are interesting, but it should be appreciated that many patients requiring repeated transfusions have systemic disorders responsible *per se* for hypoalbuminemia Knights & Hutchins (31) could find no relationship between a positive C-reactive protein test in a group of random donors and minor transfusion reactions in their respective recipients. However, they did note that all patients experiencing reactions with chills subsequently developed a positive C-reactive protein test. The efficiency with which antihistamines modify these nonspecific reactions remains controversial despite a number of reports supporting their value (13, 14). Dahlquist *et al.* (13) conducted studies with the addition of pyribenzamine hydrochloride and chlorpheniramine maleate to the donor blood. They noted a 75 per cent reduction in allergic reaction rate. In another report (14) 10 mg. of chlorpheniramine maleate added to the blood given to 2785 patients reduced allergic reactions from 1 4 per cent to .07 per cent, and pyrogenic reactions from 3 01 per cent to 0 54 per cent. On the other hand, Hobsley (12) observed no statistically significant reduction of febrile reactions to transfusions with 10 mg of chlorpheniramine maleate in a smaller series of patients. Under the conditions of any of these studies no adverse reactions to added antihistamine have been noted, but it should be emphasized that moderate to severe idiosyncratic reactions occasionally are observed (32). These consist of drowsiness, stupor, confusion, apnea, and even convulsions. Diphenhydramine (Benadryl) added to donor blood in concentrations of ten or more times those conventionally employed will produce significant shortening of erythrocyte survival (33).

Reactions caused by bacterial contamination of blood may be identical in their initial stages to the so called nonspecific reactions, and may closely simulate an acute hemolytic response The importance of recognizing each of these entities early necessitates discontinuance of transfusion with careful investigation of the circumstances before proceeding with further transfusion. From 3 per cent to 6 per cent of glass bottle blood in storage will have

bacterial contamination introduced at the time of either skin or bottle puncture. Careful attention to aseptic technique has reduced the incidence of bacterial reaction from 5.2 per cent to 0.6 per cent in Czechoslovakia (34). Bang & Paaby (35) found 11 of 100 units of blood bank blood to contain bacterial contaminants. The organisms were detected by direct smear in three of them. The degree of contamination was directly related to the storage time, and as a consequence of this they have reduced the permissible storage time from 21 to 14 days. Walter *et al.* (36) report a sixfold reduction in the contamination of blood collected in plastic bags and a reaction rate of 0.73 per cent. Their unique culture technique consisted of refilling the integral tube with mixed blood and sealing with a dielectric sealer a short segment of tubing which subsequently was cut off for culture. This procedure eliminated the necessity for bottle opening with its associated danger of contamination. Braude (37) has presented an excellent review of the recognition and treatment of transfusion reactions from contaminated blood. He notes that about 80 per cent of the organisms responsible are of the coliform-Pseudomonas group. At 4°C the Pseudomonas organisms grow well while the coliform organisms grow poorly, but survive. Reactions consisting of fever, hypotension, and pain rapidly progress to collapse and renal failure with almost invariable death. These reactions are caused by bacterial endotoxin which appears to produce a severe loss of arterial tone. For treatment Braude suggests the prompt administration of intravenous fluids, tetracycline, *l*-norepinephrine, steroids, electrolytes, and blood if necessary. For prophylaxis he suggests a time reduction in the room temperature storage of blood, microscopic examination of smeared donor blood for bacteria, and the routine use of a tetracycline antibiotic in the blood bottle. James & Stokes (38), however, demonstrated that there was little advantage in terms of growth of organisms from rapid refrigeration of collected blood. Non-refrigerator transportation of donor blood over seven years has yielded 500,000 bottles with only 1 death arising from cold-growing organisms.

Another important immediate type of transfusion reaction is that which follows overtransfusion with resultant rapid expansion of the circulating blood volume. In patients with anoxic or other types of myocardial dysfunction excessive transfusion may progress rapidly to acute pulmonary edema. In a recent excellent review of the subject Downs (39) states that "circulatory overloading is now probably the most common cause of death from transfusions when proper methods are employed to prevent incompatibilities." He described the clinical picture of acute pulmonary edema and points out that auricular fibrillation may develop, and that if the patient survives he may have considerable peripheral edema. He advocates frequent auscultation of the chest, close check of pulse, and determination of the venous and arterial pressures when large volumes of blood are infused rapidly. If pulmonary edema develops, immediate phlebotomy should be performed, so as to remove the amount overtransfused, and tourniquets should be applied to all extremities. Ancillary procedures of value are the

use of positive pressure oxygen by mask, tracheal aspiration, and fluid restriction. In another study Hornbein & Roos (40) found that transfusion of normal male subjects from hematocrits of 45 per cent to 60 per cent resulted in decreased ventilation during exercise. Pretransfusion blood volume determinations would be of infinite value in estimating transfusion requirements. Freeman (41) has found the radioactive iodinated serum albumin blood volume technique to be of value in making measurements on 209 seriously ill patients. He advocates use of either a 1 or 5 min sample In spite of these observations, it is difficult to believe that blood volume determinations of this type are very accurate under these conditions. Lack of a steady-state, inadequate mixing, and unknown alterations in small vessel hematocrit present incalculable obstacles to accurate blood volume estimation Overtransfusion of injured (42) and normal (43, 44) experimental animals has induced selective organ or tissue trapping of red cells with rapid extravascular diffusion of plasma Substantial differences in small vessel hematocrits near sites of injury would tend to increase the inaccuracy of blood volume measurements Careful clinical judgment probably is the best practical guide to transfusion requirements at the present time.

Massive transfusion-induced hemorrhagic disorders develop from a variety of causes, the chief of which are thrombocytopenia, hypofibrinogenemia, reduction in plasma labile factor and AHF concentrations, and increased fibrinolytic activity. Krevans & Jackson (45) were the first to point out that transfusion of adults, infants, and dogs for the purpose of correcting blood loss induces thrombocytopenia, the severity of which is related to the rate and amount of blood transfused. Initially, this appeared to be the result of simple dilution with nonviable donor platelets Later these investigators (46) studied the hemorrhagic disorders of two patients who had received some incompatible blood. They noted hypofibrinogenemia, thrombocytopenia, and hypoprothrombinema without increased fibrinolytic activity. They concluded that these changes probably were caused by the release of thromboplastinlike substances from hemolyzed red cells Mustard (47) in a study of 62 multiply-transfused surgical patients noted thrombocytopenia in about 50 per cent, and expressed the opinion that the combination of dilution and increased thromboplastic activity of stored blood were responsible for the reduced platelet concentrations This impression has received additional confirmation in dogs (48). Stefanini (49) has emphasized the importance of increased fibrinolytic activity in some massively transfused surgical patients The importance of this problem also has been stressed by Howland (50) in a brief review of the subject

An inordinate amount of attention has been focused recently on the adverse clinical effects of the excessive citrate administration which accompanies extensive blood replacement (51 to 60) Firt & Hejhal (51, 52) believe that overloading and heart failure during rapid transfusion is not a function of volume per se, but of the amount of citrate given In small doses citrate is said to produce pulmonary vasoconstriction, and in large doses it is said

to depress myocardial activity. They believe that the advantage of arterial transfusion is related to the rapid interstitial diffusion of citrate so that the lung and heart concentrations are lower. The adverse citrate effects can be counteracted with intravenous procaine and calcium. Bunker (53) points out that excessive citrate will chelate ionized calcium and lead to tetany, cardiac arrest, and incoagulability of the blood. Patients with liver disease or impaired liver blood flow are increased risks. He suggests the intravenous administration of calcium chloride in order to neutralize these effects. An extremely important measure for the prophylaxis of this entity is rapid stoppage of bleeding to reduce the necessity for blood (54). In spite of these reports, however, the importance of citrate toxicity in adults is unclear. Extensive investigation of this subject in massively transfused surgical patients has failed to incriminate citrate toxicity as a major problem (55, 56). No alterations in clotting mechanisms or correlation of plasma citrate levels with capillary oozing were found. Some prolongation of the Q-T interval, and increased serum potassium and total calcium were the major effects of excessive citrate infusion. These authors believed that this probably was not a hazard in adults, but might be in infants, hypothermic patients, and in patients with either disturbed calcium metabolism or liver disease. Another study of citrate toxicity in dogs and man (58) also failed to substantiate the belief that it is of any major practical importance. These investigators found slightly elevated serum sodium and depressed serum calcium levels following citrate infusion, and thought that the electrocardiographic changes resulted more from anemia than citrate toxicity The opinion also has been expressed that more deaths with massive transfusion result from overtransfusion than from the adverse effects of excess citrate (57). Avoidance of this problem in infants subjected to exchange transfusion has been advocated through the use of either heparinized (61) or exchange resin-collected blood (62) Silicone-coated glass bottles containing 1500 I U. of heparin per 500 ml of blood were used.

Widespread performance of open heart surgery has reintroduced an old transfusion hazard· that of air embolization. Nichols *et al.* (63) reported an instance of massive air embolism with recovery in a patient undergoing open cardiotomy using a pump-oxygenator and complete cardiac bypass It was the impression of these authors that air embolization constitutes a problem in the use of pump-oxygenerators which should receive serious consideration.

Transfusion Hazards of the Delayed Type

The delayed types of adverse reactions to blood transfusions are summarized in Table II. A major unsolved problem is that of homologous serum hepatitis virus transmission In pooled plasma the incidence of resultant infection is from 5 per cent to 20 per cent (11), and in a random blood donor population the incidence of active virus is about 1 in 200 The two principal approaches to the eventual elimination of this menace have been the screen-

TABLE II

DELAYED ADVERSE REACTIONS TO BLOOD TRANSFUSIONS

Type of Reaction	Manifestations	Cause
Hepatitis	Fever, jaundice, hepatomegaly, anorexia, etc.	Homologous serum hepatitis virus
Iron storage disease	Skin pigmentation, hepatomegaly, diabetes, cardiac failure, etc.	Long standing tissue hemosiderosis from multiple transfusions
Bacterial sepsis	Clinical and laboratory manifestations of specific infection	Malaria, syphilis, brucellosis, leishmaniasis, etc
Serum sickness	Fever, arthralgia, urticaria, lymphadenopathy, etc.	Probable antibody reaction of delayed type to foreign protein.
Erythroblastosis fetalis	Jaundice, anemia, shock, death	Erythrocyte isoimmunization
Erythrocyte isoimmunization	None unless transfused or pregnant	Previous erythrocyte sensitization of recipient
Platelet isoimmunization	None unless transfused	Previous platelet sensitization of recipient
Leukocyte isoimmunization	None unless transfused	Previous leukocyte sensitization of recipient
Venous thromboses	Obliterated veins	Previous venipunctures and transfusions

ing of donors and the destruction of the virus in plasma and blood. Neither has been entirely successful to date. Norris & Hunter (64) have confirmed the impression that proved carriers of viral hepatitis have a high incidence of positive thymol turbidity and thymol flocculation tests. Unfortunately, these reactions are quite nonspecific, and it appears that one or more of the hepatic function tests may become abnormal before a variety of diseases occur (65). The C-reactive protein test has been found to be useless as a screening procedure (31). Room temperature storage of plasma for periods of 6 months or longer appears to eliminate the hepatitis virus. Plasma obtained from 3846 donors was stored in this fashion and no hepatitis developed in a total of 197 recipients of this plasma (66) Large amounts of plasma free of hepatitis virus have been obtained by means of repeated plasmaphoresis from a small group of donors by means of the Cohn fractionator (67). The red cells were returned to each donor and 200 ml. of plasma was retained. *Beta-propriolactone (BPL)* has been found to be a potent virucidal agent in plasma (68). Since 1952 these investigators have administered over 1000 units of plasma treated with either BPL alone or BPL plus irradiation without causing hepatitis and without reaction Electron irradiation of plasma of sufficient energy to destroy virus produces minor plasma changes, but fairly extensive erythrocyte injury (69). Impressive virus inhibition has been demonstrated in plasma and blood subjected to 2200 atm.

of pressure at −18°C. (70). This treatment again produces severe erythrocyte injury, but the plasma remains well preserved. Some of the most promising results with virus alteration and destruction have been with heat-treated plasma preparations. This procedure tends to denature protein moderately (71, 72, 73), but the resultant product has good osmotic pressure, is not pyrogenic, and seems well tolerated by recipients. The results of these investigations indicate that practical methods for virus elimination from plasma, but not whole blood, should be available in the very near future.

Isoimmunization of female patients by means of transfusion is responsible for many fetal deaths later in life (74). Increased awareness and improved methods for the detection of isoimmunization to the rarer blood groups emphasized the potential magnitude of this problem in prospective mothers (75 to 78).

Although there appear to be few new developments relating to the transfusion hemochromatosis which follows multiple transfusions, the potential debility from this disorder is serious enough to deserve re-emphasis (79, 80, 81). The development of this disorder may be delayed or prevented in patients with refractory anemias through the judicious use of blood. Effective removal of substantial amounts of storage iron through chelation and excretion remains impractical (82).

Transfusion Emergencies

The value of blood and plasma in the management of hypovolemic shock is clearly established. For isolated or a limited number of emergencies group specific blood and plasma usually will be used, but for more major disasters plasma expanders occupy a position of greater importance Albumin is superior to dextran, expecially since four units of dextran will produce thrombocytopenia in about 20 per cent of adults (83). Thrombocytopenia results in these individuals from the coating of platelets followed by their removal from circulation. In dogs (84) injections of dextran produce red cell aggregation and slowing of the circulation, thrombocytopenia, leukopenia, and hypofibrinogenemia. Studies in experimental traumatic shock (85) have shown decreased survival of the traumatized dogs following infusions of dextran. As a temporary expedient, however, the administration of a few units of dextran may sustain a patient until blood arrives. In the initial phases of a major catastrophe, when blood grouping and crossmatching are impossible, of necessity, group O, Rh negative blood must be used In certain emergency situations Rh negative patients may get Rh positive blood unless the patient is a female in the child-bearing group, or the patient was sensitized previously (86) Witebsky states that under these circumstances it is better to have a living, sensitized patient than a dead, unsensitized one.

The quantities of red cell replacement required in burned patients have been considered by Topley (87). She feels that if more than 1 per cent of

microcytes are present in the head of the blood smear on admission the patient should have at least 20 per cent replacement of the calculated normal red cell mass followed by a blood volume study 24 hr. later. It would seem likely that rapid intravascular removal of the microcytic red cells might introduce an appreciable source of error, but this may be a useful test.

Special Types of Transfusion Therapy

The indications for exchange transfusion now seem clear, and its efficiency in reducing mortality and morbidity in erythroblastosis fetalis is evident (88, 89). The chief indication for exchange is an early rise of serum bilirubin toward critical levels (20 mg per cent) and particularly within the first 12 hr. (89). The problem of citrate toxicity in these infants has prompted investigation of heparin as an anticoagulant. Valentine (61, 90) has performed 21 exchange transfusions with heparinized blood in newborn infants without incident He also feels that the increased hematocrit of the donor blood is an advantage High hematocrit blood in the form of packed cells (91) was used in 24 infants, and blood volume studies revealed absence of the red cell deficit usually found with whole blood. Fetal sepsis (92), and unexplained cardiac deaths (93) during exchange transfusion have been cited Andre *et al* (94) have described the development of visceral leishmaniasis in a newborn infant following exchange transfusion with the blood of an adult who had cutaneous leishmaniasis Farquhar & Smith (95) have attempted to describe the clinical and biochemical changes which develop during exchange *transfusion They found increased blood citrate and potassium* levels with a fall in ionizable calcium (not corrected by calcium gluconate). Other causes of clinical disturbance were interference with circulation during the period of postnatal readjustment, excessive speed of exchange, changing blood viscosity, catheter manipulation, injection of cool blood, and inexperience.

Exchange transfusion is rapidly assuming prominence in the therapy of certain acute toxemias, particularly salicylate (96) and methyl salicylate (97, 98) poisoning in children. In these reports it is pointed out that oil of wintergreen is 98 per cent methyl salicylate and that the fatality rate from this type of poisoning is from 49 to 62 per cent Single exchange transfusions with from one to two times the calculated blood volumes of these children produced a 40 to 59 per cent reduction of blood salicylate levels and led to eventual complete recovery Exchange transfusion also has been advocated for acute poisoning with carbon monoxide, boric acid, and isoniazid. Hughes (99) and others (100, 101) have described the use of exchange transfusion in the management of patients with anuria Hughes states that cold, stored erythrocytes in the presence of glucose will take up potassium when warmed, and that they should take up excess serum potassium when given to hyperkalemic patients. Actually, there is no clinical evidence for this, and the anemic patient exchanged by Hughes showed a rise in serum potassium 12

of pressure at −18°C. (70). This treatment again produces severe erythrocyte injury, but the plasma remains well preserved. Some of the most promising results with virus alteration and destruction have been with heat-treated plasma preparations This procedure tends to denature protein moderately (71, 72, 73), but the resultant product has good osmotic pressure, is not pyrogenic, and seems well tolerated by recipients. The results of these investigations indicate that practical methods for virus elimination from plasma, but not whole blood, should be available in the very near future.

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taken into consideration. Plasma and blood transfusions to patients with a deficiency of certain coagulation factors are an important form of transfusion therapy. It has been noted, however, that not infrequently *in vivo* activity and concentration for a specific clotting factor are considerably below *in vitro* estimates. This has been described in PTA deficiency (114), with the use of serum in PTC deficiency (115), and following the administration of plasma to AHG-deficient patients (116). Transfusion of whole blood, platelet concentrates (117), or preserved platelets (118) may be of considerable hemostatic value in platelet deficiency syndromes.

A new era for transfusion therapy is unfolding rapidly in the form of open-heart surgery Unique and severe demands on the blood bank, hematologist, and donor population are being imposed. Experience at the Mayo Clinic with 400 operations using the pump oxygenator has exposed some of the problems (119). Of 15,000 units of blood used at the Clinic annually, 3000 (20 per cent) are used by the machine alone The oxygenator uses from six to nine units of heparinized blood per patient, and from one to four units of ACD blood are kept in reserve. No intergroup crossmatching is performed and no intergroup incompatibility has been encountered. Each operation is planned months ahead, and to date no donor has failed to arrive at 7.00 a m. on the day of operation. The only test performed at the end of each operation is a plasma hemoglobin No major hematologic complications have been encountered, but air embolization has been reported elsewhere (63). At the Cleveland Clinic, Battle & Hewlett (120) have studied the hematologic changes in 12 patients following open-heart surgery. A rotating disc oxygenator was used for periods of 9 to 24 min. They noted minimal hemolysis of erythrocytes at the conclusion of the procedure followed by a slight reticulocytosis one week later. Ten of 12 patients showed a moderate granulocytic leukocytosis, and five patients subsequently exhibited some atypical lymphocytes There was a slight fall in blood platelets during the first three postoperative days in four patients. None of the patients had excessive bleeding in spite of minor coagulation changes

IN VITRO STORAGE AND *IN VIVO* SURVIVAL OF BLOOD

An important storage lesion of red cells consists of interference with intracellular production of organic high energy phosphates and the accumulation of inorganic phosphate salts Addition of certain purine nucleosides will modify this defective metabolic pathway *in vitro*, and the changes noted are associated with enhanced *in vivo* erythrocyte survival The addition of inosine delays the structural breakdown of red cells (121). Kashket *et al.* (122) have found that the addition of nucleoside tends to maintain the glycolytic capacity of the red cell even though the nucleoside itself retards utilization of glucose Donohue *et al.* (123, 124) have demonstrated that both adenosine and inosine have prolonged the storage of usable blood. Inosine, in contrast to adenosine, is converted to hypoxanthine and then to uric

hr. later followed by a drop 40 hr. after exchange. A single patient with severe hepatitis and coma has been extensively exchanged on two occasions with eventual recovery (102). Exchange transfusion of four schizophrenic patients produced no significant change in their mental status (103).

The technique and indications for large artery, usually intra-abdominal, perfusion in the management of 13 surgical emergencies with good results have been described (104, 105). The surgeons introduced a curved needle into the lower aorta and infused from 500 to 1000 ml. of blood without complication. The adventitia was perfused with 1 per cent procaine at the end of the procedure in order to avert ischemic change due to vasoconstriction. A needle method for passing a nylon tube into the femoral vein has been described (106). No complications were encountered in 14 patients following infusions of blood, glucose, electrolytes, 50 per cent dextrose, and nitrogen mustard, even when the catheter was left in place for a period of six days Wrench & Dique (107) have given reverse transfusions into the distal segment of leg veins whose proximal segment was obliterated by burns, tight dressings, or thrombosis. Intraperitoneal administration of blood has been recommended for patients, especially children, with chronic blood loss or inadequate erythropoiesis (108, 109). Red cells in the peritoneal cavity are rapidly and almost completely transported via the thoracic duct into the general circulation where they have normal survival. In West Africa, 43 successful infusions of this type have been given to 36 children with kwashiorkor for the purpose of correcting anemia and supplying nutrition (110).

A rather unusual suggestion for transfusion therapy includes the use of blood transfusions in the treatment of the postgastrectomy (dumping) syndrome (111) These investigators believe that rapid fluid loss into the stomach following ingestion of a hypertonic meal produces hypovolemic change with its associated syncope Pre- and postprandial blood volume studies corroborated this impression, and indicated that patients with low blood volumes were most susceptible Blood transfusions and plasma expanders greatly modified the unpleasant symptoms in these patients. Elliott (112) found marked reductions in plasma and red cell volumes in patients with acute pancreatitis within the first 24 hr. This was believed to be caused by a suffusion of plasma around the pancreas, and to increased erythrocyte fragility with hemolysis following the release of pancreatic trypsin. He believes that the liberal early use of blood and albumin has helped reduce the mortality from 19.5 per cent in 1952 to the present figure of 6 5 per cent. Repeated transfusions of packed red cells to patients with sickle cell anemia depresses the bone marrow so that eventually mostly normal red cells are found in the peripheral blood (113). This procedure has been found to be of value in managing surgical and leg ulcer patients with this disorder Limited personal experience with this method of healing leg ulcers has been disappointing. Furthermore, the danger of accelerating the development of hemochromatosis in patients with chronic hemolytic anemia should be

the preservation of platelets (49, 139, 140, 141). Wurzel & Johnston (139) found that with careful collection of blood to prevent clotting, 40 per cent of the platelets were present in bank blood after 21 days. Marked platelet morphologic changes were noted after 3 to 4 days in storage. There was 50 per cent survival of the labile factor at seven days. McIlvanie (140) has found plastic bags, glass bottles, and siliconized glass bottles about equal in maintaining biologically active platelets, but has found plastic bags extremely useful in the preparation of platelet-rich plasma. Nour-Eldin & Wilkinson (115) have indicated that PTC may deteriorate rather rapidly in storage at 4°C. and even −25°C. They noted a rapid loss of Christmas factor activity of −25°C.-stored plasma after the seventh day and no activity at two weeks No activity was found in dried plasma made from plasma stored at 4°C. for 17 to 20 days. Plasma stored at 4°C. for less than five days was recommended for treatment in order to insure good PTC activity

Increased erythrocyte destruction in recipients receiving compatible blood occasionally is observed (142, 143). Mollison & Cutbush (143) suggest the use of isotope-labelled donor cells as a test of biological compatibility in instances where recipient serum gives weak serologic reactions or when antibody incompatibility is suspected. Their procedure is to label 1.0 ml of donor blood with 30 μc of Cr^{51} and then to determine the biological half-time survival of this blood in the recipient. Mollison & Hughes Jones (144) have found that very rapidly removed red cells (2 to 6 min half-time) localize predominantly in the liver whereas cells removed more slowly (20 min half-time) localize predominantly in the spleen.

Transfused platelets have shown a blood survival of about six to seven days (20, 140) in thrombocytopenic recipients with conventional counting techniques. Platelet survival studies with Cr^{51}-labeled platelets show normal survival to be in the 9 to 11-day range (145) During the first 24 hr., plasma activity continues to rise, suggesting transient sequestration of the infused platelets Chromium-51-tagged human and rabbit platelets have been studied for their tissue distribution (146). Most of the activity, 20 min. postinjection, is found in the liver and spleen of normal rabbits. If the rabbits are sensitized previously with platelets, however, most of the activity is found in the lungs This mechanism for platelet removal is very similar to that noted for leukocytes in leukocyte-sensitized rabbits. Tullis (147) has transfused platelets obtained from ACD blood by means of the Cohn fractionator. He obtained a 50 per cent yield of platelets by this method A rise in recipient platelet count was noted from 1 to 7 hr posttransfusion, and this was associated with improved capillary fragility, decreased bleeding, and increased prothrombin consumption. Antihemophilic globulin assays following plasma infusions into hemophilic patients indicate a biological half-life of 9 hr. for AHG (116) Rapid disappearance of PTC was observed in a patient with Christmas disease so that improvement in thromboplastin generation was gone 24 hr postinfusion (115).

acid. Its use in stored blood increases blood uric acid levels and uric acid excretion in the recipient. Gibson *et al.* (125) have evaluated a citrate-phosphate-dextrose (CPD) solution for the preservation of blood Post-transfusion percentage viability of CPD-stored red cells in plastic bags was increased as compared to those stored in ACD despite higher concentrations of inorganic phosphate Peeters (126) believes that sodium lactate has advantages over sodium citrate for red cell storage, but no survival data are presented to support this concept. The ammonia content of stored blood increases with time so that by the twenty-first day the concentration is about 250 µg./100 ml (127). Transfusion of a liter of this blood would produce clinically insignificant change in blood ammonia. The advantages of blood collection and storage in plastic bags (125, 128) has been challenged by Dudley *et al.* (129) who believe that the overall performance in plastic is no better than glass. Minor advantages consisting of weight saving, volume saving, integral pilot tube, and reduced danger of air embolism were noted. These authors evaluated neither bacterial contamination nor the effects of turbulence and foaming on ultimate erythrocyte preservation. Strumia has focused attention on the importance of the immediate collection damage of red cells which develops as soon as red cells are placed in acid (acid shock) (130). This affects about 6 per cent of the red cells, and is not altered by glass or siliconized surfaces. Unfavorable surfaces in contact with red cells will induce additional damage, however (124, 125, 131).

Low temperature storage of red cells holds great promise for the future, but these techniques still remain a long way from routine use. Ketchel *et al.* (132) have reported their results of glycerol-stored blood at −80°C for periods of six months to one year. Only 2 per cent of the red cells were lost in the processing of 200 units of blood with the Cohn fractionator. No bacterial contamination was encountered and posttransfusion red cell survival ranged from 79 to 90 per cent At −20°C glycerol-stored cells slowly deteriorate, but at −45°C. there is a virtual arrest of metabolism (133). Chaplin *et al* (134) have obtained excellent results (95 per cent posttransfusion survival) with cells stored in buffered citrate glycerol at −45°C. Atraumatic removal of glycerol from the red cells has been a major problem, but several new methods (135, 136) have been devised to improve this process A comprehensive evaluation of red cells stored at temperatures ranging from 10°C. to −20°C indicates that 4°C is best for routine use (137). A technique for rapid freezing and storage of blood in liquid nitrogen (−198°C.) has been described (138). These preliminary results appear encouraging, but the practical problems of storage and sterility remain to be overcome.

Good storage preservation of protein clotting factors and platelets depends to a considerable extent on the prevention of minor clotting which may occur during collection and storage (139). There is fairly good general agreement that plastic and silicone surfaces are somewhat better than glass for

Summary

Rapid progress in the fields of cardiovascular surgery, blood clotting, and immunohematology have necessitated increased use of blood transfusion therapy, and have imposed stringent demands on the laboratory control of a blood transfusion service. Improved methods of blood preservation eventually may obviate some of the problems of supply and demand. It is hoped that increased awareness and understanding of transfusion reactions will reduce the waste and misuse of transfusion therapy. The current morbidity and mortality rates from transfusion are of such a magnitude that absolute necessity must be the basis for every unit of blood administered.

The Hospital Blood Transfusion Service

Camp (148) has emphasized that the background for a safe blood transfusion service depends on a continuous training program. He has outlined the necessary requirements for a successful blood bank as follows: (*a*) strict adherence to reagent instructions; (*b*) an understanding of genetic terms by all personnel; (*c*) a refresher training course for all medical personnel; (*d*) decision and resolution of immunologic problems by a physician; (*e*) emphasis on confirmation tests; (*f*) adoption of current technical changes, (*g*) avoidance of contaminated reagents; and (*h*) the checking and rechecking of all steps from donor bleeding to issue of blood. Other measures advocated are the use of a good blood tagging system, nonuse of pilot tubes, and transportation of samples and blood under laboratory control (8) These points are emphasized since so much of the legal responsibility (5, 10, 11, 149) and success of a transfusion service depends upon the laboratory. A number of technical procedures have been designed to expedite and improve laboratory services. The use of pressure tape labels (150) and pilot tubes firmly attached to bottles (151) could be of great value. Khuns & Ridley (152) have demonstrated that abnormal plasma proteins, especially cryoglobulins, may cause rapid slide agglutination at 37°C. The reaction is not reversed with saline, and therefore the authors advocate the use of washed or diluted red cell methods The detection of rare antibodies presents another problem for which there is no easy solution at the present time. Papain-treated, pooled red cells are said to be valuable in the detection of Rh and Hr antibodies (153). Crowley *et al.* (154) point out that anti-M is active at low temperature and they suggest routine crossmatching at 4°C. Sussman (155) believes that a high protein test supplemented by the antiglobulin test should detect practically all reactions. Young (156) believes that the ideal crossmatch should be simple, easily performed, highly sensitive, and good for an emergency. He advocates use of a highly sensitive trypsin-saline test for both routine and emergency compatibility testing, but also thinks that the "10 minute albumin test" is a valuable emergency procedure

A good transfusion service is not possible without an adequate supply of blood, and this depends on having a large donor population. A well-organized collection center such as that designed and reported by Carroll *et al.* (157) should greatly facilitate the collection of blood and improve donor morale Alsever (158) has put much thought into the problem of minimum hemoglobin requirements for donors, and holds that the standard should be uniform and at the level of 12.5 gm per cent for males and 12 0 gm. per cent for [illegible] the iron lost

be given in a year. An iron tolerance test has been successfully employed for the detection of masked iron deficiency in blood donors (160).

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DISEASES OF THE SKIN[1]

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This review will cover, as space permits, those areas of dermatology which have attracted the most interest in the last year. Subjects discussed in the preceding *Annual Review of Medicine* will not be reviewed again unless significant new material has been presented.

THERAPY OF SKIN DISEASES

The search for more potent steroids which will produce fewer side effects continues Methylprednisolone (Medrol) and triamcinolone (Aristocort, Kenacort) are the newest members of this expanding group. Baer & Witten (1) and Rein *et al* (2) state that both of these chemicals are more effective in the treatment of skin diseases than prednisolone and have less effect on sodium and potassium metabolism. Triamcinolone (3) has proven temporarily beneficial to many psoriatic patients (60 per cent clearing on 8 to 16 mg. a day). Dubois (4) found that it provided adequate control in lupus erythematosus These newer steroids have not been used long enough to be fully evaluated Neither methylprednisolone nor triamcinolone produces fluid retention (patients tend to lose weight while taking triamcinolone). The most serious side effect reported for triamcinolone (4) is muscle weakness This steroid produces greater cutaneous reactions; Cushingoid appearance, hirsutism, and striae are more marked than with other steroids A peculiar flushing and hyperhidrosis following the ingestion of triamcinolone has occurred in a few patients (3)

There has been no significant addition to the topically applied steroids. A controlled clinical study by Frolow, Witten & Sulzberger (5) has shown that 0 5 per cent prednisone, 0 5 per cent prednisolone, and 1 per cent hydrocortisone ointments have equal therapeutic effect. Robin & Kepecs (6) found that topical hydrocortisone applied to normal skin did not alter the itching produced by stroking the skin. Frank (7) showed that hydrocortisone applied to stripped skin prevented histamine-induced pruritis. These studies again emphasize that the therapeutic effect of topical steroids will vary with their ability to penetrate into the skin Hydrocortisone sodium succinate and hydrocortisone acetate solutions have been injected into cutaneous lesions by Savitt (8). This therapeutic technique may prove beneficial when there are few lesions and when the steroid ointments are ineffective. While hydrocortisone itself has never produced allergic dermatitis this reaction may occur from the use of hydrocortisone ointment. Identification of the offending

[1] The survey of the literature pertaining to this review was completed in July, 1958

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reported by Hobbs & Calnan (21) are more disturbing. This reaction is less transient than the others and appears to lead to a loss of visual acuity. More study is necessary before the full implications are determined.

The changing social patterns in the United States have accentuated the problem of intolerance to sunlight. While 8-methoxypsoralen (8-MOP) was originally used in the treatment of vitiligo (29) some patients reported increased resistance to sunlight and increased tanning (30, 31, 32) after its use. Patients in a controlled, double blind study, however (33), were unable to differentiate between 8-MOP and a placebo This result probably indicates that there was a defect in the mechanism of the investigation since 8-MOP is unquestionably a potent photosensitizer. The histologic changes produced in the skin by 8-MOP and sunlight have been studied (34, 35). After the skin has been sensitized (oral ingestion of 20 mg of 8-MOP 2 hr. before exposure to sunlight) sunlight in suberythema doses produces a reaction in the skin leading to the formation of a dense, adherent, stratum corneum. The lower portion of the stratum corneum is eosinophilic and resembles the stratum lucidum of the palms and soles. This dense eosinophilic zone protects the skin against sunburning. This reaction of the psoralens has been used to protect patients with light allergy. The psoralens should be considered when patients are allergic to longer wavelengths (36) or intolerant to antimalarial drugs. In previous studies Lerner *et al* (29) found that 8-MOP had no effect on the enzyme tyrosinase. In recent histologic studies (34, 35) no increase in pigment formation was observed Following the change in the horny layer, there was, however, an increased retention of melanin in the adherent stratum corneum and in the basal cell layer This increase in the retention of melanin makes 8-MOP a true tanning agent.

There has been concern about possible liver damage following the ingestion of psoralens Elliott (37) reported abnormal liver function tests during psoralen therapy. Since these patients were not tested before starting the medication, the laboratory findings are difficult to interpret. There have been no further reports of similar findings. In a recent study by Fitzpatrick, Imbrie & Labby (38), individuals were given 30 mg. of 8-MOP daily for three months. No abnormality of the thymol turbidity, zinc turbidity, cephalin cholesterol flocculation, or sulfobromophthalein tests was found

The use of monobenzyl ether of hydroquinone in the therapy of hyperpigmentation was discussed in the preceding issue of this *Review*. Ito (39) first described a peculiar type of depigmentation (leucomelanoderma) following the use of this product. There have been subsequent reports by others (40, 41). The patients applied a preparation containing 2 to 20 per cent monobenzyl ether of hydroquinone for some time. They developed a dermatitis and when the irritation subsided irregular depigmentation followed. This reaction is not common and its mechanism is not understood. It is well to warn patients using this chemical that treatment should be stopped if there is dermatitis or rapid irregular lightening or darkening of color.

material is frequently impossible since the exact formula of the commercial ointment is often a trade secret. Swarts (9) has recently emphasized this problem.

The antimalarials have been used in the therapy of lupus erythematosus and light allergy since Prokeptchauk's original report (10). Those most commonly used and their daily dose are (11): quinacrine (Atabrine, mepacrine) 100 to 300 mg.; chloroquine (Aralen, nivaquine) 250 to 750 mg.; hydroxychloroquine (Plaquinol), 400 to 1200 mg. These three antimalarials have also been used in combination by Rein & Fleischmajer (12). Amodiaquin (Camoquin) 200 to 300 mg. has been used less extensively (13).

Cahn, Levy & Shaffer (14) showed that chloroquine did not affect the minimal erythema dose of ultraviolet light in normal skin or in patients with papular polymorphous light eruption. They have amplified their work (15) and shown that the antimalarials concentrate more in the epidermis than in the dermis. These chemicals did not form a significant barrier to the passage of ultraviolet light through the separated epidermis. The clinical effect of the antimalarials cannot be caused by light screening. In animal studies these chemicals were found in the skin and liver (16) but no information has yet been published concerning any specific action at these sites. Other animal experiments (17) have shown that quinacrine protected animals against histamine. This was not attributed to an antihistamine action. The animals had increased secretion of 17-ketosteroids and hypertrophied adrenal glands. Stimulation of the adrenal glands could explain the therapeutic effect the antimalarials have in many different diseases. It has also been shown by Holman & Kunkel (18) that quinacrine prevented the combination of the lupus erythematosus serum factor with cell nuclei. The antimalarials apparently have several modes of action.

The antimalarials are relatively nontoxic in the small doses used to treat malaria. When larger doses are used toxic reactions may occur. The following effects have been reported recently:

Quinacrine. The yellowing of the skin, lichen planuslike eruption, sweat retention, and toxic eruptions of quinacrine are well known.

Chloroquine Acute porphyria and coproporphyrinuria (19), acute exfoliative dermatitis (20), granular deposits in the cornea (21), bleaching of hair (22), lichen planuslike eruption (23)

Amodiaquin: Amenorrhea, partial blindness and yellow pigmentation (24), yellow color and increased melanin pigmentation of the skin (25).

Hydroxychloroquine · Nervousness, toxic eruption, intestinal cramps, and hoarseness (26)

Combination. (quinacrine, chloroquine, and hydroxychloroquine) diarrhea, vertigo, diplopia, nausea, and muscle pains (12).

Since quinacrine and amodiaquin are yellow compounds one would expect the skin to turn yellow when high doses are used. Disturbances of vision caused by synthetic antimalarials have previously been reported (27, 28). The insidious, sometimes asymptomatic deposits in the corneal epithelium

placed in the area of male and female gonads The amount of radiation reaching the gonads was found to be small. These investigators next sought methods of further reducing the gonadal radiation. Increasing the distance between the x-ray tube and the patient, reducing the voltage, decreasing the size of the irradiated field, covering the patient with a lead-rubber sheet, and the use of a cone all appreciably reduced the gonadal dose

PATHOGENETIC AND CLINICAL CONSIDERATIONS

The development of a granulomatous reaction in the axillae following the use of deodorant sticks containing sodium zirconium lactate was reported in the previous issue of this *Review* (55, 56). Since this chemical has been removed from cosmetic preparations, the disease has disappeared Shelley & Hurley (57) have found the mechanism of this reaction to be an allergic reaction to zirconium. The sensitizing material (deodorant stick) had to contain at least 4 per cent sodium zirconium lactate The axillae had to be shaved before the material was applied. The minute defects in the skin produced by shaving allowed entry of the sodium zirconium lactate into the skin After this material was applied over a prolonged period, some individuals developed the granulomatous reaction They were tested for sensitivity by injecting 0 02 ml of a 10^{-4} 10^{-6} dilute solution of sodium zirconium lactate into the skin. The test was considered positive if a persistent noninflammatory papule developed after a latent period of several days. Patients who reacted to sodium zirconium lactate were found to react as readily to zirconium chloride or zirconium nitrate. It was shown, therefore, that minute amounts of a simple metallic ion could produce a granulomatous response in the skin. The authors feel that the Mitsuda and Kveim test might be explained on the basis of specific antigens present in trace amounts. Kooij & Gerritsen (58), however, believe the Mitsuda and Kveim reactions are of a foreign body type, depending upon injections of particles The concept of allergy to trace amounts of simple ions certainly will receive more attention.

The danger of precipitating a melanoma by electrodesiccation or incomplete removal of nevi has been argued for years Walton, Sage & Farber (59) have begun a study which should help solve this problem. One hundred sixty-eight pigmented lesions were removed from 82 subjects These lesions were removed superficially and the area was electrodesiccated The treated areas were rebiopsied in 112 lesions at intervals from three to twelve months. No evidence of malignant degeneration was found. These patients will continue to be observed. Schoenfeld & Pinkus (60) report the pathologic study of 19 cases in which pigmentation occurred after incomplete removal of nevi No evidence was found of any malignant change in these lesions.

Becker, Sr. (61) reviewed the various pigmented lesions of the skin. When melanomas develop in an ordinary nevus, the malignant change occurs in the superficial portion of the nevus (dermoepidermal junction). If this portion of the lesion is removed, the nevus cells which may be left in the

In the field of systemic fungus infections, Cornbleet (42) has added thyroid to the iodides commonly used for the treatment of deep mycoses Favorable results are reported in blastomycosis and sporotrichosis Amphotericin B is a crystalline product derived from a species of *Streptomyces* originally found in South America. This product has *in vitro* antifungal activity against *Candida albicans, Candida neoformans, Blastomyces dermatitidis, Blastomyces brasiliensis, Sportotrichum schenkii*, and *Histoplasma capsulatum*. Encouraging therapeutic effects have been reported in North American blastomycosis which was resistant to stilbamidine (43), cryptococcosis (44), and coccidiodomycosis (45)

Planing of the skin for various dermatologic conditions has continued to evoke interest. The focus of interest has shifted, however. Epstein (46) discusses the use of planing in the treatment of senile skin with precancerous lesions. While some physicians are enthusiastic, this approach is condemned by others. This therapy is based on the belief that skin cancer arises from a chronically damaged epidermis. Microscopic examinations of senile skin always reveals changes in the dermis It is impossible to renovate the deeper layers of the skin and time alone will tell whether growing a new epidermis on top of an altered dermis will significantly reduce skin cancer.

Burks (47) reports that dermabrasion is capable of completely and permanently removing the fingerprint pattern from the palmar skin. This finding at present has more legal than medical significance.

The problem of antibiotic-resistant bacteria and the question of using antibiotics in combination are of current interest in dermatology as well as other specialities. An editorial (48) concluded than when more than one antibiotic is used it is better for the physician to establish the ratio rather than to use a commercial preparation with a fixed ratio of antibiotics

Safety has always been a consideration in the use of x-ray therapy. In the past physicians have been concerned with the amount of radiation which would permanently damage tissue, or the amount of scattered radiation which would adversely effect the health of the operator Landauer (49) presents the changing viewpoint of the therapist to safe doses of x-irradiation. Domonkos & Cameron (50) reviewed the exposure of operators of x-ray therapy machines They list methods of screening and changes in technique which will protect the operator.

Recently, stimulated by increase in background radiation, concern has arisen about the amount of radiation reaching the gonads and its effect on future generations It is difficult to determine the amount of gonadal radiation which will affect future children The committee on Genetic Effects of Radiation of the National Academy of Sciences (51) has recommended that the amount of man-made radiation reaching the gonads from birth to age 30 be not more than 10 roentgens Witten, Sulzberger & Stewart (51 to 54) have investigated the amount of radiation reaching the gonads during the usual type of x-ray therapy used by dermatologists A wood phantom placed in various positions was used to simulate the patient and a dosimeter was

placed in the area of male and female gonads. The amount of radiation reaching the gonads was found to be small. These investigators next sought methods of further reducing the gonadal radiation Increasing the distance between the x-ray tube and the patient, reducing the voltage, decreasing the size of the irradiated field, covering the patient with a lead-rubber sheet, and the use of a cone all appreciably reduced the gonadal dose.

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dermis have no malignant potential. Clinical diagnosis of pigmented lesions is inadequate. All suspicious pigmented lesions (those that are growing, changing color or shape, have bled or become friable, or have recently appeared in an adult) should be examined microscopically after removal. Caro (62) presented a discussion of an adequate skin biopsy technique.

Two apparent entities (benign pemphigoid and subcorneal pustular dermatosis) have recently been separated from the large group of blistering diseases. "Ocular pemphigus" (scarring of the conjunctiva) has been recognized as a nonspecific reaction which is not related to pemphigus vulgaris Lever (63, 64) reported patients in whom this reaction in the eyes was associated with blisters or other lesions on the skin and mucous membranes Lesions resembling lupus erythematosus (65) and lesions of the penis and vulva (66) have been reported by others. Lever (67) separated this disease from true pemphigus and called it "benign mucous membrane pemphigoid." Brunsting & Perry (68) and Degos *et al* (66) have discussed more patients and further characterized the disease.

This disease occurs primarily in the elderly The average age of onset in one series was 60 years (67) While this disease was originally studied in patients with eye lesions, many of the most recently reported patients have had neither eye nor mucous membrane lesions. Most of the patients reported by Brunsting & Perry (68) had had previous allergic diseases The eruption in these patients consisted mainly of itchy patches of blisters located on the face or neck. These blisters left superficial scarring when healed. Only one patient had occasional lesions in the mouth and he had had conjunctival disease previously Two patients developed a generalized blistering eruption. Clinically, the disease was marked by a chronic course with exacerbations and remissions and a poor response to therapy

Histologically, the lesion consisted of a subepidermal bulla without acanthalysis. Most of the biopsy specimens showed edema of the dermis with a dense cellular infiltrate in which eosinophils predominated.

No evidence of virus infections was found and these patients did not react to patch tests of KI, KBr, and KCNS as might be expected in patients with dermatitis herpetiformis

It is impossible to be certain at this time that all of these patients represent exactly the same disease. There appears to be no question, however, that there are skin and mucous membrane lesions associated with "ocular pemphigus" and that these lesions may precede the eye lesions or may occur without eye lesions. This disease has been discussed under the titles of "benign mucous membrane pemphigoid," "?benign pemphigoid," and "dermatose bulleuse mucosynechante et atrophiante."

Sneddon & Wilkinson (69) first described the entity of subcorneal pustular dermatosis in 1956 Greenbaum & Lee (70) have reviewed the previously reported examples of this disease and discussed the eruption in their patient. This disease appears to occur primarily in women over the age of 40. Clini-

cally, it resembles dermatitis herpetiformis and consists of plaques of itchy pustules. Microscopically, the pustule was seen to lie just beneath the stratum corneum and to be filled with neutrophils. These lesions are usually sterile and there has been a varying response to therapy.

Dermatitis of the hands commonly originates under a ring. When patch tests are done many of these individuals do not react to the metals present in the ring. Gaul (71) has presented evidence to indicate that in some instances the reaction to jewelry or other metal objects is due to a primary irritation. The irritating material results from a reaction of the salt present on the surface of the skin with the metals and alloys of jewelry.

There is some evidence to indicate that systemic lupus erythematosus is increasing (72). Holman & Kunkel (18) learned that the L.E. factor from the serum of patients with lupus erythematosus had an affinity for cell nuclei. Holborow, Weir & Johnson (73) also demonstrated this affinity and concluded that the L.E. factor had the nature of an antibody. Robbins, Deicher & Kunkel (74) investigated the removal of complement during the reaction between serum from patients with lupus erythematosus and cell nuclei and deoxyribonucleic acid (DNA). The complement disappeared during both reactions. Cross absorption experiments, however, suggested the presence of two factors. The factor responsible for the formation of the L.E. cell is responsible for complement fixation with nuclei. The factor which fixes complement with DNA appears to be a different material.

There is as yet no single diagnostic test which is 100 per cent accurate in the diagnosis of lupus erythematosus. Slepyan *et al* (75) found that the ratio of bound/free pantothenic acid was low in both discoid and systemic lupus erythematosus (another hint that these are variants of one disease). Jones & Thompson (76) have reported a precipitin test which appears to be fairly specific for lupus erythematosus. It is logical to assume that a battery of tests (L. E. cell preparation, bound/free pantothenic acid level, and precipitin test) would provide a better laboratory diagnostic index than any single test.

No disease is more clothed in myth or superstition than *Rhus* (poison ivy, oak, sumac) dermatitis. In two outstanding articles (77, 78) Kligman (extensively quoting the excellent work of Shelmire, McNair, and others) supplies a solid base of fact. *Rhus radicans* (poison ivy), *Rhus toxicodendron* (poison oak), and *Rhus vernix* (poison sumac) produce identical reactions in the skin. The antigenic components of poison ivy consist of four catechols. The less reactive 3-pentadecylcatechol has been synthesized and used for quantitative testing.

Ivy dermatitis is produced only when the sap from the plant touches the skin of a sensitive individual The plant sap may be carried by smoke, on clothing, or animal fur. No human being is born sensitive to poison ivy but every individual will become sensitive if there is adequate exposure. Sensitivity tends to decrease with age

No great advances have been made in local therapy and topical prophylaxis has very little effect. The systemic steroids have proven valuable in very severe dermatitis.

The eventual solution of ivy dermatitis lies in desensitization of the allergic individual. Kligman attempted controlled desensitization with several materials. Maximum hyposensitization with oleoresin was obtained with 2000 to 2500 mg. intramuscularly or 2500 to 3000 mg. orally. Pentadecylcatechol required 2500 to 3000 mg. intramuscularly or 3500 to 4000 mg. orally to obtain the same result. Kligman states that alum-precipitated pyridine extracts of poison ivy plants appear to be biologically inert. Hyposensitization was not easily accomplished, was only partial, and proved to be temporary.

Psoriasis is a common skin disease which has aroused the interest of physicians for many years. Michelson (79) discusses the unusual clinical aspects of psoriasis. Norins & Yaffee (80) presented a patient suffering from rare psoriasis of the hard palate. Ingram (81) reviewed the three chronic pustular eruptions of the hands and feet (acrodermatitis continue, pustular bacterid, and pustular psoriasis). Of the 133 patients with pustular eruptions, 35 had psoriasis and 98 did not. Forty-four of the patients with pustular eruptions were male and 89 were female, and the average age of onset was between 40 to 50 years (range 7 to 70 years). The precipitating factors were nonspecific (trauma, infection, toxic, or emotional stress) Ingram feels that these diseases are variants of a single reaction pattern.

Laboratory investigation of psoriasis has been very extensive but, unfortunately, most of the findings have been disappointing. Examination of the exocrine pancreatic fluid in the duodenum of psoriatic patients revealed no abnormality (82). No significant correlation was found between abnormal levels of lipides, serum proteins, and lipoproteins and the existence of psoriasis (83). Under controlled metabolic conditions, two psoriatic patients showed no evidence of nitrogen retention (this differs from the results obtained by Schamberg in 1913). There was no abnormality in the urinary excretion of sulfur by these psoriatic patients (84). There are interesting observations since the psoriatic patient loses sulfur and nitrogen in the scale. Study of free-moving-boundary electrophoresis of the serum in members of a family containing three psoriatic individuals revealed no serum protein abnormalities attributable to psoriasis (85)

Shelley & Arthur (86) have reviewed the biochemical and physiological information concerning psoriasis. The most promising investigations at present deal with the cutaneous enzyme systems. Enzyme determinations have shown that the psoriatic lesion has low dipeptidase activity. This may arise either from an inhibitory factor in the psoriatic scale or lack of an enzyme activator (87) Flesch & Esoda (87, 88) have shown that as a result of this defective enzyme metabolism, the water-soluble fraction of the psoriatic scale is low in free amino nitrogen, has a high sulfhydryl content, has decreased water-binding capacity, and impaired ability to allow fluids to pass

through a column of pulverized scales. The Koebner phenomenon (precipitation of a psoriatic lesion in the skin of a psoriatic patient by trauma) has also been investigated (89, 90). After superficial trauma, the skin of these patients exhibits a greater dehydrogenase activity than the skin of normal individuals The finding of specific enzymatic and metabolic disturbances presents a solid basis for continued study. No such encouraging advance has been made in therapy. Harber (91) has made a controlled study of the effect of x-ray therapy in psoriasis. Goldberg (92) reports the failure of L-lysine monochloride as a therapeutic agent for psoriasis

During the descriptive phase of dermatology many diseases were isolated on the basis of minute clinical or histological detail. This trend has now been reversed and some of these diseases are no longer considered specific entities Van Ketel (93), on the basis of clinical and histological examinations, has concluded that rosacea, like tuberculid of Lewandowsky, has no connection with tuberculosis and is actually acne rosacea Jabłońska *et al.* (94) and Lutz (95), in several recent articles, have concluded that epidermodysplasia verruciformis is simply disseminated flat warts occurring in specially reactive skin The feeling is growing that many diseases are more attributable to the soil provided by the individual than the eliciting substance or organism. Ingram (96) discusses the seborrheic diathesis and Barlow & Chattaway (97) consider the philosophy of fungus infection.

INVESTIGATIVE STUDIES

Recent research in dermatology has encompassed so many subjects that only a few can be mentioned here Rostenberg & Gonzalez (98) have investigated a new and probably more physiologic method of controlling perspiration. Lobitz (99), Montagna & Formisano (100), and Mustakallio (101) have shown, using histochemical methods, that succinic acid dehydrogenase activity is increased in the sweat ducts during eccrine sweating. Utilizing the known inhibitory effect of the malonate ion for succinic acid dehydrogenase, Rostenberg and Gonzalez applied an ointment containing 20 per cent sodium malonate and inhibited eccrine sweating

Greenberg & Cornbleet (102) studied the reaction of the skin of men and rats following the application or intradermal injection of a carrot-oil, water-solubilized suspension of carotene. Using frozen sections and a fluorescent microscope they found yellow fluorescence (presumably carotene) in the sebaceous gland cells and a fading green fluorescence (presumably vitamin A) in the neck of the sebaceous glands and spread in a thin film on the surface of the skin. These fluorescent materials appeared within 30 min. of the in-injection of carotene. Patients with pityriasis rubra pilaris, ichthyosis, and psoriasis were studied (103). The uninvolved areas of skin in these patients reacted as did normal skin. Areas of pityriasis rubra pilaris and ichthyosis had no fluorescent material within the sebaceous glands and areas of psoriasis had much less than in normal skin.

Interest has continued in all phases of pigment formation The pigment-

forming cells of the skin (melanocytes) are difficult to stain and many questions concerning their physiology and anatomy are still being debated Staricco (104) repeated previous studies (105, 106) which described the reaction of melanocytes following stimulation with thorium X. He found that all the brown pigment (melanin) was produced in the melanocytes. Basal cells had no pigment-forming ability and were not converted into melanocytes. Quevedo, Lewis & Smith (107) have shown that melanocytes are not derived from mast cells. Staricco noted an increase in the melanocytes following stimulation and observed migration of some melanocytes toward the surface of the epidermis. He confirmed previous work which indicated that the melanin does not enter the basal cells after this type of stimulation.

Breathnach (108, 109, 110) has counted the melanocytes in human forearm skin and studied the distribution in forearm skin of freckled subjects He also investigated tyrosinase activity in the melanocytes of freckled skin. Kropp (111) observed the melanocytes of skin which had been stripped with plastic tape. Szabo (112) estimated the tyrosinase activity of melanocytes in preparations of separated epidermis from white skin. He found a variation in the number of cells containing active enzyme in skin from various areas of the body. Tukamoto & Taniguchi (113) compared the inhibitory effects of various compounds on *in vitro* tyrosinase. Harris & Lerner (114) have determined the amino acid sequence of the α-melanocyte-stimulating hormone. They also investigated the β-melanocyte-stimulating hormone. The amino acid sequence of these hormones was very similar to the sequence of some of the amino acids in corticotropin

One of the major functions of the epidermis is the production of stratum corneum (horny layer) This very complex layer bears the brunt of all external irritation. As has been previously mentioned (34, 35) the stratum corneum provides the primary protection against the burning rays of the sun. Electrolytes do not penetrate the normal skin readily and various theories concerning a specific single electrolyte barrier have been proposed. Monash (115) has shown that practically the entire thickness of the stratum corneum acts as a barrier. There has been disagreement about the exact composition and formation of the stratum corneum. Lustig, Katchen & Reiss (116) analyzed the nitrogen, sulfur, ash, lipoid content, and amino acid composition of calluses and of scales derived from psoriasis, exfoliative dermatitis, and disseminated neurodermatitis Flesch (117) presented current concepts on the formation of the stratum corneum Butcher (118) observed the effects of various externally applied materials on keratinization.

Rothman & Lorincz (119), in a special report, lucidly summarize the wealth of research material presented at the Hair Conference in London

Externally applied therapeutic agents are being manufactured in ever increasing numbers. It is often difficult to decide whether these new preparations have any advantage over currently popular materials. Kinmont (120) discusses the aims, techniques, and statistical analysis necessary for the valid comparison of two externally applied therapeutic agents.

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PEDIATRICS[1]
(NONCARDIAC ANOMALIES)

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The year was not marked by developments of such stature as might be comparable to the demonstration that congenital tracheoesophageal fistula with esophageal atresia is susceptible of correction, or that Hirschsprung's disease could be effectively treated by the resection of the narrow segment which has proved to be aganglionic. However, the volume of pediatric surgical writing, and especially that writing dealing with congenital anomalies, continues to increase steadily

GENERAL

Rickham (1) points out that 42 per cent of 405 infants operated upon as newborns for congenital anomalies had been prematurely born, and that in these the mortality was 42 per cent, as opposed to 17 per cent in the full term infant. The mortality was directly related to maturity (i e., birth weight), since for the premature above 2000 gm , there was a 26 per cent mortality, whereas, below 2000 gm the mortality was 64 per cent. The chief causes of death were respiratory problems (i.e., pneumonia and atelectasis), problems of surgical technique, widespread bleeding despite administration of vitamin K, and severe cardiac malformations. Great stress was laid on the necessity for turning the children frequently from one side to the other, to allow each lung, beneath the soft chest wall, to expand fully

Browne (2) analyzes the development of ring constrictions of the extremities. Streeter, in 1930, in dispelling the notion that these constrictions might result from pressure of one limb on another or constriction by an umbilical cord, suggested localized necrosis and failure in development as causative factors In what appears to be a reversion to the acceptance of a purely mechanical process, he suggests that the limb bud protrudes through a hole in the amnion and is constricted by it. No such protrusion has ever been noticed at birth, but it may be too much to hope that such an amnion would be preserved However, strips of tissue resembling amniotic membrane have occasionally been found in such ring constrictions and the amnion has been noted to appear shredded in such cases. The children, generally, are otherwise normal except for an increased frequency of club foot deformity. The two most telling points are the increased frequency of ring constrictions towards the ends of the extremities and the fact that the digits are frequently fused in this deformity, with the ring about both fused

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closure of the lip at a single operation when the child weighs twelve to fourteen pounds.

Thoroughgood & Fischer (12) continue to argue for the repair of cleft lips on the first day of birth. It is true that from the standpoint of lip repair, in most cases this almost certainly is satisfactory. However, it may not give time for the recognition of other anomalies and in these patients who may require, particularly in the presence of associated palatal clefts, years of treatment and education, there may be some virtue in allowing the mother to see the original defect as a base line for her future observations.

The Children's Medical Center in Boston stresses teamwork for the repair of cleft lips and palates. They report 2635 operations performed for cleft lips and palates from 1942 to 1957 without a death (13).

The dental problems associated with cleft lips are those arising from congenital maldevelopment, surgical trauma, and dental caries (14). Wiring procedures or other forcible closures of a wide maxillary cleft, are the commonest surgical causes of dental distortion in early infancy. In unilateral clefts early orthodontia is frequently indicated. In bilateral clefts, however, if the anterior teeth are poorly formed, orthodontia is futile, and when the child reaches adolescence, extractions and prosthetic appliances are required.

The number of surgical techniques for the correction of micrognathia of the mandible indicates that difficulties exist in all the procedures. Robinson (15) presents a new method for the correction of this defect involving vertical osteotomy of the ascending ramus, with iliac bone graft.

It is not widely recognized that newborn babies, with complete nasal obstruction, may die of asphyxia soon after their birth because of inability to breathe through the mouth If they do survive there may be difficulty in eating, so that the child may die of starvation before it masters the technique of alternate breathing and swallowing Bilateral atresia of the nasal choanae is a rare cause of such obstructions and, when it occurs, may be associated with other deformities of the nasal passages, eyes, and lids (16) Basically, the diagnosis may be suspected in infants with severe cyclic dyspnea or in infants with dyspnea while suckling. In older children excessive nasal discharge and tears which discharge from the anterior nares during crying are suggestive of the diagnosis. A transpalatine perforation into the nasal passage, with use of a palatal mucosal flap, gives good results.

Huppler & Beahrs (17) point out the frequent hereditary occurrence of branchial cleft fistulae. They found 18 patients with fistulae in a family numbering 49 members.

Congenital goiter is rarely seen in this country, and more rarely still operated upon. In two sons of a woman in whom there was no history of maternal medication with thiourea or cobalt, signs of obstruction developed; cyanosis and respiratory obstruction were seen in one, with difficulty in swallowing exhibited by the other. Subtotal thyroidectomy produced relief in both children and despite the suggestions made in previous reports, neither child developed myxedema (18).

digits. Kelikian & Doumanian (3) discuss malformation of the hand but are unable to illustrate any specific etiological factors. They suggest that surgical interference should be early, but only if it enhances function.

Gruenwald (4) strengthens the argument that the cause of many congenital deformities may not be a failure of development of a structure but a necrosis of the structure after it has been formed. The increasing number of reports of the presence of lanugo hairs and vernix squames distal to intestinal atresia provide clinical support for this theory. In Gruenwald's experiments, the injection of selenium into chick eggs which were sectioned at intervals of one-half to five days, was said to produce necrosis of cells in already established portions of the embryo. This necrosis occurred in such well-defined areas as the brain, the cord, the optic cups, the lens, the limb buds, and the somites of the tail region. The areas of necrosis correspond with the malformations seen in older embryos. This necrosis may be the prime mechanism in the production of defects with secondary effects of this failure of development being felt by surrounding structures. The agent and the time of its action determine the nature of the anomaly.

The association of maternal rubella in the first trimester of pregnancy, with the appearance of congenital deformities in the infants resulting from these pregnancies, has been widely accepted since the Australian reports made by Gregg in 1941, and Swann in 1943. The validity of such purely retrospective studies is challenged in a prospective study of 103 women diagnosed by a physician as having rubella during pregnancy in the first trimester, and followed until the resultant children could be examined (5). Whereas retrospective studies suggested an incidence of anomalies of the brain, heart, eyes, and ears of 50 to 100 per cent, prospective studies show an incidence of 12 per cent, with an additional 7.2 per cent of still births. While there is some increased risk of congenital deformity in liveborn babies of mothers having rubella during the first trimester of pregnancy, this is thought not to be an absolute indication for therapeutic abortion

Descriptions of congenital anomalies continue to be plentiful. Wilson (6) describes a Marfan syndrome kinship, involving eight individuals in three generations with defects of the skeletal and cardiovascular systems No information about the basis for the defects was obtained from this study. A case of anhidrotic ectodermal dysplasia in a 15-month-old white male infant with vascular nonthrombocytopenic purpura is presented (7). Gargoylism is discussed and four cases in the American negro are reported (8, 9). These are believed to be the first documented examples in this racial group.

Face and Neck

In the repair of cleft lips there appears to be agreement that complete preservation of the prolabium, including all of the vermilion border, is of importance (10, 11). Cronin (10) points out that, if necessary, a preliminary recession of the markedly protruding maxilla, with Kirschner-wire fixation to the vomer, may be done at three to four weeks, permitting subsequent

closure of the lip at a single operation when the child weighs twelve to fourteen pounds.

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CHEST, LUNGS AND MEDIASTINUM

Esophageal atresia and esophageal fistula occur once in 2500 to 3000 live births. The diagnosis is made in the newborn exhibiting respiratory difficulty, in whom esophageal intubation is impossible. Whereas there is no general agreement among surgeons as to the use of the retropleural or transpleural approaches, there is a perceptible shift towards the transpleural operation as being easier for the surgeon (19). The mortality is much higher in the type of atresia which presents a very short, or absent, distal esophageal segment. Thirty-seven of ninety typical cases died, and nine of eleven atypical cases died (20). The extremely rare and fatal anomaly of a tracheoesophageal fistula in which the atresia is of the trachea is described by Devenis & Otis (21).

An instance of total atresia of the distal esophagus, without tracheo-esophageal fistula, was successfully treated by a one-stage right thoracotomy with an elevation of the stomach into the chest and an anastomosis to the proximal segment (22). A rare case of tracheoesophageal fistula without esophageal atresia is reported by Kraus & White (23).

Congenital absence of pulmonary tissue may vary from agenesis, the complete absence of bronchus and lung, through aplasia in which there is a rudimentary bronchus without surrounding parenchyma, to hypoplasia in which there is a bronchus with a rudimentary underdeveloped lung (24). Agenesis may be lobar or pulmonary. Both may be asymptomatic, but deviations of the normal anatomy in the remaining lung are common and may account for symptoms when they exist. In one child with repeated pulmonary infections, agenesis of the upper lobe and stenosis of the intermediate bronchus were found. Treatment consisted of resection of the middle and lower lobes, with relief of the symptoms (24).

The sternum develops embryologically from paired longitudinal bands which fuse by the ninth week. These may fail entirely of fusion, or may fuse only in their more distal portions, producing a "V" shaped cleft. In either case the heart may protrude conspicuously.

The earlier reports of Maier and of Longino demonstrated the feasibility of primary repair of sternal clefts in the very small infants by direct suture of the sternal halves without any chondroplastic procedure. Sabiston (25) points out that as late as 28 months a relatively simple oblique chondrotomy of the involved cartilages of both sides permits approximation of the sternal halves.

There is a continuing interest in depression and protrusion deformities of the chest. Lester (26) reviewed 150 such cases, with 122 designated as depression deformities and 28 as protrusion ones. He states that heredity is a most important etiological factor, and that the pathogenesis is related to the size and shape of the diaphragm with disproportionate growth of the ribs. New techniques for repair have been described by Sutherland (27) and by Ekström (28), and there is continuing evidence that pectus excavatum may produce clinical signs and symptoms. Ekström (28) reports that one-third of 50 cases operated on for a funnel chest deformity had dysp-

nea, easy fatigability, and susceptibility to infections. Two-thirds of the patients had a systolic murmur and cardiac dislocation, usually to the left. He uses a rib strut of homologous bone to support the sternum after it has been elevated. In all but one patient the rib strut was absorbed in a few months, by which time the costal cartilages were claimed to have regenerated in the corrected position.

Shillitoe & Wilson (29) report a large cystic lesion in the thorax of a 15-year-old girl containing heterotopic pancreatic tissue.

Diaphragm

Paul & Kanagasuntheram (30) point out from anatomical studies of diaphragmatic hernias of the Bochdalek type, that the abdominal viscera ascend into the chest in an orderly and predictable way. The more mobile viscera enter first. The small intestine herniates before the large intestine and the large intestine before the stomach. The stomach is the last portion of the intestinal tract to enter the defect of a Bochdalek hernia, and is never found alone in such a hernia. A rare central diaphragmatic defect is described by Grossman, Brady & Stephens (31).

Engberg, Thomsen & Vesterdal (32) state there is an apparent increase in the incidence of hiatus hernia in children. This is attributed to the frequency of radiological examination of the esophagus and stomach in cases of unexplained vomiting. Between the neonatal period and the end of the second year, many hiatus hernias of the sliding type are cured spontaneously. In children above the age of two repair of the hernia is advised. Children with sliding hernias and esophageal changes cannot usually be treated by simple repair of the hernia.

Stomach

Abramson & Folston (33) and Castleton & Hatch (34) point out that gastric perforations in newborn infants, exclusive of those caused by peptic ulcer, trauma, or obstruction, arise from rupture through a congenital muscular defect. Of 40 reported cases in newborns, males predominated over females, two and one-half to one The ages at which perforation occurred ranged from eleven hours to ten days. The roentgenograms have almost always shown free air, and 23 operations were performed, with eight survivors. Vomiting or regurgitation and melena gave way to sudden distention, cyanosis, respiratory difficulty, and shock. There is adequate evidence of absence of muscular layers at the site of perforation in thirteen cases, and of thinning of the muscular layers in five. The site of perforation is recorded in 30 cases of which 22 are on the greater curvature. There were six instances of associated congenital anomalies and nine instances of prematurity (34).

Fifteen duplications of the stomach have been previously reported in the pediatric age group. Kiesewetter (35) adds another such duplication to the literature and notes that while many duplications found in other parts of the alimentary tract have an opening into the lumen of the gut, only two duplications of the stomach have been reported to have a communication.

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Total excision is suggested, but with large duplications of the stomach it may be necessary to compromise.

Gastroschisis is a congenital fissure of the abdominal wall with protrusion of the viscera without a covering membrane. The absence of a sac and the absence of herniation into the cord distinguishes this condition from omphalocele. Berman (36) presents four cases, three of whom survived, including one with intestinal atresia requiring resection and primary anastomosis.

Intestinal Obstruction

Intestinal obstruction in the newborn still carries a high mortality. Jones & Schutt (37), reviewing 130 cases over the last 20 years of alimentary tract obstruction in the newborn, recorded an increase in the number of newborn infants with intestinal tract anomalies. They noted that the poorest prognoses occur in those cases with meconium ileus, or in those with multiple anomalies; that anal malformations have the highest percentage of associated congenital anomalies (71 to 75 per cent); and that 18 per cent of infants with atresia of the alimentary tract have additional areas of obstruction. Earlier diagnosis and treatment are required to reduce further the mortality in these anomalies Their review supports the contention that temporary gastrostomy used after primary repair of esophageal atresia is beneficial

Del Junco & Franco (38) report a case of midgut volvulus with massive rectal bleeding as the initial sign. The early onset and frequency of intestinal obstruction in children with prolapse of the intestine through a completely patent omphalo mesenteric duct is taken as an indication for immediate operation for this anomaly (39). One would not suppose any urging to be necessary.

Intestinal duplications give rise to symptoms by virtue of their presence as masses causing intussusception, obstruction, or volvulus; or because of bleeding, either from pressure on the neighboring bowel, or from peptic ulceration of the neighboring bowel if the duplication contains gastric mucosa. Jewett (40) describes an ingenious operative procedure in a baby with a duplication of the entire small intestinal tract, blind proximally but communicating with the terminal ileum distally, and causing serious hemorrhage from a peptic ulcer at this point. Both ends of the duplication proved to be lined by gastric mucosa. The distal end was closed and the proximal end was anastomosed to the stomach Despite the very long blind loop the baby has been well for one and and one-half years Weatherill, Forgrave & Carpenter (41) present three cases of obstruction in the newborn caused by annular pancreas. Obstruction of the colon by congenital valves has frequently been reported. Hoffert *et al* (42) add a case in which the valve was located in the rectosigmoid area of the colon, a location which is rarely involved.

Potts and his associates (43) review pictorially the problem of intestinal obstruction in the newborn and emphasize the use of radiographic study in making the diagnosis Hope & O'Hara (44) demonstrate

x-rays and the instillation of small quantities of air into the gastrointestinal tract as diagnostic procedures in suspected intestinal obstruction of the newborn. They emphasize that opaque contrast materials and fluoroscopy are not necessary in many cases.

Hirschsprung's Disease

Interest in Hirschsprung's disease continues to be strong and the year is marked by Swenson's ten-year review of the results of his own operation in 200 cases (47). There is now universal agreement that the disease is caused by absence of the ganglion cells of the myenteric plexus, and that this absence begins in the most distal segment of the rectum and extends upward for a variable distance, occasionally including the entire intestinal tract (45 to 49). It is also generally agreed that the disease carries a lethal risk in infancy and that early colostomy should be resorted to. In Riker's series of 59 cases, 24 were recognized in the neonatal period, and twelve of these required operation during the first week of life (45) Dorman (48) has accumulated 156 proved cases of Hirschsprung's disease recognized in infants under six months, with a 48 per cent mortality. Almost one-third of the survivors were saved by a colostomy. Swenson (47) and Dorman (48) resort to proctoscopic biopsy of the bowel for confirmation of the diagnosis. Riker never employs it, although he regularly biopsies the proximal segment at the definitive operation for frozen section determination of the existence or absence of ganglion cells. If a colostomy is performed, Riker biopsies a portion of the wall of the bowel which is employed for the colostomy, and performs an extra-mucosal biopsy of the sigmoid as well. The x-ray cannot be depended upon as an accurate index of the extent of the involvement and biopsies at operation must be employed (45). Whereas Riker feels that definitive operation in newborns would be desirable if the patient's condition allows it, Swenson feels as strongly that surgery should be postponed in all cases until the patients are 12 to 18 months of age Riker, having performed a colostomy previously if necessary, operates when the babies are six months old. Swenson has operated upon 200 cases in the ten years since he first employed the operation. There have been six postoperative deaths, none of them arising from anastomotic failure. This does not include the deaths of the children who did not come to the definitive operation The fact that four of the six deaths occurred in infants has led Swenson to postpone operation until the patients are twelve to eighteen months of age. Of 73 patients evaluated at five to ten years after operation, 72 are found to be well and with no incontinence. Of 64 examined two to five years after surgery, 63 are well; and of the 52 who were operated less than two years ago, 49 are entirely well. Of the five children who are not perfectly well, only one has constipation. Eight males have married and fathered children, and none claims an ejaculatory defect. It is interesting that seven children died suddenly one to five years after operation, following a brief infectious illness of less than 24 hr duration, with severe dehydration These are not unlike the deaths which are seen fairly often in children with Hirschsprung's disease who have not been operated upon.

Malformations of the Anus

Donovan & Stanley-Brown (50) *point to the frequency of associated fistulas in newborns with imperforate anus. Urinary tract fistulas were found in 85 per cent of their male cases, while more than half of their female patients had rectovaginal fistulas.* In males, primary operation is performed at once; in females, operation is postponed by Donovan & Stanley-Brown for four to five months. Only in premature, malnourished infants is a preliminary colostomy employed. *Their technique for females involves circumcision of the vaginal fistula, drawing the rectum down, and pulling the dissected fistula through the sphincter to form a new anus. If the fistula is high in the vagina,* an abdominoperineal operation is required in females as in males. Donovan & Stanley-Brown, like most authors, *emphasize the necessity for careful* postoperative dilatation of the anus.

A more detailed analysis of the occurrence of urinary tract fistula in association with anorectal malformation is given by Nicolai (51). *In 100 anorectal anomalies he found urinary fistula in 60 per cent of the patients,* 17 of them unsuspected before operation. There were 24 rectourethral, 22 *rectovaginal, 9 rectoperineal and 5 rectovesical fistulas.* All but one of the urinary fistulas occurred in the characteristic Type III anomalies, which *comprise 77 per cent of all cases. The demonstration of the small caliber urethral fistulas which were usually in the prostatic membranous urethra was most generally achieved by a urethro-cystogram, using an aqueous* contrast medium and a blunt nosed syringe Nicolai prefers a *primary abdominoperineal pull-through procedure, without a preliminary colostomy.* The substantial mortality of 22 per cent, all before the fourth month of *life, was usually caused by associated anomalies. If a fistula persisted after the primary operation, colostomy was required for successful secondary repair*

The condition frequently described as an ectopic anus is considered by Bill, Johnson & Foster (52) *to be an anteriorly placed perineal rectal opening. The deformity may be so inconspicuous as to be overlooked until such children are brought in with constipation due to the presence of a pouch* posterior and caudal to the opening They report 14 females and 16 males, many of whom presented a *congenital median band,—a band of tissue running in the anteroposterior direction across the ectopic opening In patients* with anteriorly placed rectal openings, an anal dimple can usually be recognized, and although it may actually appear raised, *it may be made to pucker on skin prick. All patients, except the four operated upon the first day of life, were constipated in spite of fairly large anal openings in some* The ectopic opening in females tends to be further anterior than in males The *embryologic explanation offered is that the mesodermal,* perineal body tissue closes in from the sides *behind the developing rectum, producing an* [illegible] The operation recommended by [illegible] ter [illegible]. If the opening is very close to the anus an *incision is carried straight back from* the lumen of the opening to the *anal dimple and mucosa is sutured to the*

skin. Results were good, in 75 per cent of the patients. (This latter procedure resembles Dennis Browne's operation for the same condition.)

Pancreas, Spleen, Biliary System

The occurrence of portal hypertension in fibrocystic disease of the pancreas has been documented by the finding of raised sweat electrolytes, characteristic pancreatic biopsy, the history of "celiac disease," chronic pulmonary infection, massive splenomegaly, and elevated portal pressure (53). While this association has been noted before, the relationship between portal hypertension and fibrocystic disease has not been established, and hepatic insufficiency in such patients has not yet been reported.

The combination of repeated serious infections in a child with a congenital cardiac lesion suggests agenesis of the spleen, and the diagnosis may be further suggested by the presence of an increased number of erythrocytes showing Heinz inclusion bodies in the peripheral blood, increased target cells, decreased osmotic fragility. Howell-Jolly bodies, and normoblastemia (54). A case of agenesis of the spleen, congenital heart disease, and complete situs inversus is reported by Terslav (55). A total of 81 cases has been collected by Gilbert, Nishimura & Wedum (56). They add five additional cases of congenital malformation of the heart with associated splenic agenesis.

Choledochal cyst is a rare anomaly. Upward of 200 such cases have been reported The lesion is an aneurysmal dilatation of the common duct. Females are more commonly affected than males, and the symptoms are those of jaundice, pain, and a palpable mass The jaundice is usually intermittent. In reporting five cases, Grove (57) demonstrates excellent preoperative studies with intravenous cholangiograms and postoperative studies with catheter cholangiograms. Roux-en-Y anastomosis of jejunum to the cyst is preferred by Grove. In the smaller, entirely retroduodenal cysts, direct cystoduodenostomy is probably preferable

Sacrococcygeal Teratoma

These tumors are present at birth, varying in size from externally insignificant, entirely intrapelvic or intraabdominal tumors, to huge external masses causing dystocia (58). Symptoms are produced by pressure on the rectum, urethra, or ureters; by infection through the necrotic skin overlying the large tumors, and by malignant alteration which occurs in perhaps 20 per cent of cases. The treatment is immediate and complete resection.

Gynecologic Lesions

Tietz & Davis (59) report the excision of a ruptured ovarian cyst, existing at birth and removed on the first day of life. The clinical picture suggested ascites. Another successful operation was performed 48 hr. after birth in an infant with a huge ovarian cyst which did not rupture (60). Anteriorly placed vaginal cysts just at the introitus and one-half to three-quarters of an inch in diameter are described by Cohen, Kline & Laver (61).

One such was sufficiently large to obstruct the urethra and was resected, the other ruptured spontaneously and none of them recurred. These are thought to be cysts of Gärtner's ducts.

Genitourinary Lesions

Investigation and publication in this field has been extensive during the past year. Hilson (62) interestingly points out that malformed ears, particularly if asymmetrical, are quite commonly associated with congenital malformations of the genitourinary tract. These ear deformities are similar to those seen in infants with renal agenesis The genetic association between these anomalies is discussed. Sieber & Klein (63) describe two infants who were female pseudohermaphrodites of nonadrenal origin with persistent cloaca. This is a previously unreported urogenital anomaly, which, if recognized early, requires separation of the urinary and fecal streams as soon as possible for survival and for normal urinary function.

Reporting from Babies' Hospital, Lattimer (64) adds 22 cases to the literature of congenital deficiency of the abdominal musculature. He points out that since the lesion and its associated genitourinary problems have become familiar, one to three cases a year have been seen by his group Twenty of the 22 cases are males. In two cases the resultant abdominal enlargement was sufficient to cause dystocia In 85 per cent of the cases there was some evidence of obstruction to the bladder outlet and resultant megacystica, megaureter and hydronephrosis. Eighteen of the 20 males had undescended testes, usually found attached to the midureter. Malformations of an extremity were found in nine cases. Fifty per cent of the cases were dead before nineteen months and of these, seven were dead within twelve days of birth, usually of renal insufficiency. Anomalies of the gastrointestinal and cardiac systems were frequent. Therapy should be directed toward the relief of the vesical outlet obstruction and plastic procedures on the tortuous ureters.

Attention is directed by Fitch & Denman (65) to the correction of the abdominal wall defect They point out that DeBord in 1955 first described the feasibility of using multiple plicating sutures of the unopened abdominal wall for correcting laxity of the parietes. Fitch & Denman, in a six-year-old male, employed a long midline incision from xyphoid to pubis and widely overlapped the fibromuscular layers, adding a series of plicating sutures in the right upper quadrant where the abdominal wall below the skin was only $\frac{1}{16}$ of an inch in thickness The patient demonstrated ureterectasis, pyelectasis, and caliectasis on the right, with a normal urinary tract on the left, and a huge hypotonic bladder. The authors point out that their patient had had repeated upper respiratory infections and that his respiratory function studies (if these are to be depended upon in a six-year-old child), showed decreased function before operation, and improved function after operation.

In the treatment of exstrophy of the bladder, Kiefer & Linke (66) favor the procedure of ureterorectostomy and preanal colostomy. This operation, previously used in older patients with cystectomy for carcinoma of the bladder, provides an uncontaminated urinary receptacle with control of

evacuation; and for the proximal bowel, drawn down through the sphincteric ring, sphincter continence if the operation is successful. Two of Kiefer & Linke's patients were infants, so that the presence of continence in either child is still unsettled. In one patient, a three-year-old girl, urine can be retained for 3 to 4 hr. and there is continence of both ureteral orifices and no ureteral dilatation.

Despite the general dissatisfaction with the results of ureterosigmoid implants, the occasional case does brilliantly, as demonstrated by one with normal kidneys and ureters 38 years after operation (67). Regardless of the method of dealing with exstrophy, all agree that the bladder should be removed if it is not actually employed in the repair, in order to prevent the inevitable development of carcinoma Once the exstrophy of the bladder has been repaired, reconstruction of the hypospadiac penis poses a problem. Hinman (68) points out the necessity, after urinary diversion has been achieved, for closure of the ventral abdominal defect, removal of the vesical mucosa, release of the dorsal angulation of the penis, and formation of an adequate urethra with preservation of the prostatic ducts Scrotal flaps are employed to complete the urethroplasty. Most of his patients had a rectosigmoidostomy although, in common with the present trend, he now prefers either an ileal conduit, or a rectal bladder with the distal sigmoid drawn down through the sphincter anterior to the anus. Culp (69) reports that urethroplasty in patients with hypospadias will yield unsatisfactory results unless all chordee has been corrected, usually at a previous operation. He prefers to correct the chordee at eighteen months and delays urethroplasty until successful correction of the chordee has been demonstrated The urethroplasty may be performed six months after the operation for chordee, and at all events should be performed before the child reaches school age. Culp modifies the operation according to the deformity. In scrotal-perineal hypospadias the Dennis Browne technique is the procedure of choice, whereas, in the penile and penoscrotal hypospadias, the two-stage operation of Cecil is preferred. Of 105 cases carried to completion and cure, 40 needed additional procedures after those originally planned (69).

A detailed study of the embryologic development of exstrophy of the bladder and hypospadias was presented by Glenister (70) Exstrophy of the bladder is a linear midline cleft of the anterior abdominal wall, opening directly into the bladder. Males always have a gutter of mucous membrane extending continuously from the inferior angle of the trigone to the tip of the glans. In each case the recti in their sheaths are intact. Since, at no stage, does the urogenital sinus open on the abdominal wall, exstrophy of the bladder must represent the result of a rupture of structures and not of arrested development. Paul and Kanagasuntheram in 1956, postulated that mesoderm invading the *infra* umbilical abdominal wall, fails to fuse and leaves a persistent linear midline membrane where ectoderm of the abdominal wall and entoderm of the urogenital sinus are in contact. If this membrane undergoes dissolution, a cleft is produced, bounded by the rectus sheath. Wyburn in 1937, on the other hand, attributes the deformity to a

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verumontanum was found in all five cases and, being a part of the prostate, this naturally shares in its enlargement.

Although cystometric studies did not prove particularly helpful in the study of congenital vesical neck obstruction (74), cineradiography of congenital vesical neck obstructions and megaureters appears to have been one of the most revealing methods of study employed (75). Posteroanterior and oblique cine films taken before and during micturition, after injection of sterile barium sulfate suspension or 35 per cent iodopyracet compound (Diodrast Compound), permits analysis of events in micturition. In the megaureter-megacystitis syndrome, a large smooth bladder is found Vesicoureteral reflux occurs in all, at rest or on micturition. There is distention of the ureters and upper tracts on micturition and a large ureteral residue, but no vesical residue. The bladder contraction is normal in all cases. After micturition, with a patient remaining in the erect position, the ureters remain briefly filled with contrast material, showing tight contraction of ureterovesical junctions. The ureters then empty into the bladder. After two or three successive voidings the contrast material is finally discharged All of these ureters showed very vigorous peristalsis. Edwards disagrees with Swenson's theory of faulty parasympathetic innervation, incomplete bladder emptying, incomplete vesical neck opening, and diminished contractions of the lower ureters, since none of these are seen in his studies The absence of any histological abnormality of the innervation of the ureters in Bodian's finding further supports Edward's observations.

Despite all that has been written about congenital bladder neck obstruction and megaureter, at least one profound student of the subject is uncertain of the nature of the entity (76). Hypertrophy of the bladder neck, for instance, may be seen endoscopically with obstruction attributed to distal lesions such as valves, diverticula, etc. The hypertrophy appears to be part of the general detrusor hypertrophy. The group studied consisted of 48 children less than ten years old, all of whom had either a large residual urine, vesical diverticula, trabeculated bladder, or ureteral dilation. No cases of cord bladders were included; however, most had renal impairment. In one group of males under three years of age, Williams (76) noted chronic retention, small thick bladders, evidence of obstruction of the whole posterior urethra, rigidity of the urethral wall, and fibroelastosis of the urethra. These children developed some incontinence after vesical neck resection. The best cases, from the standpoint of therapy, were those with large diverticula which could be excised It is suggested, therefore, that these diverticula were the cause of the symptoms and that diverticula may result from normal bladder contracture through a muscular defect in the vesical wall. Another group of children were reported, both males and females, with chronic retention, large, lax bladders, and large ureteral orifices with free reflux for whom bladder neck resection was not helpful. These were thought to be the retention phase of the megaureter-megacystitis syndrome. These ureters gape widely, but do contract. The bladders are trabeculated and true retention may ultimately follow. There is no fibroelastosis. Finally, there are

deficiency of mesoderm from the primitive streak which normally sweeps round the margins of the caudal part of the cloacal membrane and invades the allantoic extension of the membrane. In either explanation the ectoderm and entoderm remain in contact and the thin membrane disintegrates, leaving the bladder open. Glenister (70) suggests that two types of mesoderm are involved, the somites and the unsegmented lateral plate mesoderm, both ultimately derived from the primitive streak. The mesoderm of Paul and Kanagasuntheram is the somite mesoderm of the lower thoracic region, whereas that of Wyburn is the lateral plate mesoderm. When bifid penis occurs, it results from failure of the pair of phallic tubercles to meet in the midline. Hypospadias is caused by varying degrees of failure of urethral groove formation, and failure to fuse on the part of the urethral folds.

The occurrence and significance of vesicoureteral reflux in children occupied the attention of a number of urological clinics. Headstream & Jones (71), examining children with no urological disorders and using a voiding cystourethrogram found, among 100 children age fourteen days to fourteen years, only one child with a vesicoureteral reflux. In this four-month-old infant, admitted for malnutrition, cystoscopy showed a bladder neck contracture and moderate trabeculation. On the other hand, in 455 children among whom the cause of admission to the hospital was enuresis in 430 cases and urinary tract infection in ten, similar studies by Forsythe & Whelan (72) revealed 61 patients in whom reflux into one or both ureters was found on a voiding cystourethrogram (Sterile barium sulfate suspension was employed.) In 17 of the 61, some ureteral dilatation was found; seven presented a posterior urethral valve; and in one, vesical neck hypertrophy was demonstrated. Two of the dilated ureters were found in children with obstructive uropathy There remained 30 children who showed vesicoureteral reflux in an otherwise apparently normal urinary tract. However, these were all patients who had been seen by urologists for urinary tract symptoms.

The pathology of vesical neck obstruction was studied by Bodian (73) in five infants dying with bladder neck obstruction The structures were fixed *in situ* with formalin and sectioned so that sections included the base of the bladder, the entire urethra, and the prostate. Control cases were similarly sectioned. In these patients they found consistently a decrease in musculoglandular elements, and increased prominence of fibroelastic elements, and an enlargement of the prostate along the entire prostatic membranous urethra, from a submucous collar at the bladder neck to the corpora spongiosa. There was no difference in the scatter of ganglia. Secondary vesical muscular hypertrophy extended to the anterior wall of the posterior urethra as far as the verumontanum. Bodian suggests that fibroelastosis of the elongated prostatic tissue causes partial or complete obstruction over a long urethral segment from the bladder neck to the distal membranous urethra, where it may be maximal because of particularly prominent fibroelastosis below the level of the verumontanum. The obstruction is primarily below the bladder neck and involves a long segment of urethra. Hypertrophy of the

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some cases of simple megaureter without strictures and *without reflux*, without retention, but with enuresis. This appears to be a functional obstruction at the lower end of the ureter. Williams (76) is also unable to accept Swenson's aperistaltic theory and feels that absence of peristalsis is a late consequence.

Deakin (77) finds that, in children without ureteral dilatation (and in the absence of neurogenic lesions), who are thought to have a vesical neck obstruction, relatively simple transurethral manipulations suffice for relief. Once there is extensive ureteral reflux and ureterectasis, Deakin employs the unorthodox technique of T-tube drainage of the ureters, even for months at a time, the upper arm of the T reaching the renal pelvis Subsequently, bladder neck resection may be done and the result checked by temporary closure of the T tube. Deakin stresses the necessity for relief of the kidneys in these children with long-standing ureterectasis before employing distal corrective procedures.

Congenital unilateral cystic kidney is differentiated from the polycystic kidney in being unilateral and in presenting a gross anatomical disorganization In polycystic kidneys, both kidneys form enlarged masses, usually causing symptoms later in life as a result of gradual dilatation of the numerous small cysts with destruction of the remaining parenchyma. In unilateral multicystic kidneys, the ureter is poorly developed, or absent, little or no normal parenchyma can be identified, and there is evidence of congenital malformation with the presence of islands of cartilage in the abnormal renal substance. Numerous cases are reported (78 to 81).

Of 108 newborn boys with one or both testes incompletely descended, 89 of the involved gonads descended in the first twelve months (82). Surgical intervention for hernia performed on a number of these revealed that the path of the scrotum was blocked by a definite fibrous barrier and Scorer *feels that it is this which prevents descent of the testes. Therefore,* operation early in infancy to remove this fibrous barrier will allow descent of the testes. Of eleven such cases of cryptorchidism, operated upon under *the age of three months, ten showed good results.*

Miscellaneous

Thompson, Straub & Arnold (83), in reviewing 31 cases of congenital absence of the fibula, find a fibrous band in the calf which appears to play a most important part in producing the bony deformity of the tibia associated with this anomaly. Excision of the band is advised

There are increasing reports of conjoined twins and attempts at separation. Aird states that annually there are born perhaps six conjoined twins, capable of surgical separation. Actually, of every 82,000 deliveries, there will

liver is recorded (84). Separation of the infants was performed ... death of one of the *twins. The remaining infant died* six hours after the operation from a cardiac anomaly incompatible with life.

DISEASES OF THE RESPIRATORY SYSTEM[1,2]

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Introduction

This review of recent literature on respiratory diseases is necessarily selective. The diagnosis, treatment, epidemiology, and prevention of pulmonary tuberculosis are reviewed. Theories of the pathogenesis of diffuse obstructive emphysema are reviewed and present-day treatment is discussed. Other subjects covered are bacterial and viral pneumonias, fungus diseases, suppurative diseases, sarcoidosis, cancer, and miscellaneous conditions, including some newly described pulmonary diseases. The pathology of tuberculosis and the effects of treatment on tuberculous tissue are well covered in a fine monograph (155).

Pulmonary Tuberculosis

Some years ago 50 to 90 per cent of adults in most parts of the world reacted to tuberculin. Except in infancy and childhood, the test was then of little practical value in the diagnosis of the disease. Today, the incidence of reactors among school children in the United States ranges between 2 and 10 per cent and, among adults living in large cities, between 15 and 50 per cent (78). The tuberculin test has thus become a useful tool in diagnosis as well as in case-finding surveys In order to avoid unnecessary radiation exposure, it is now recommended that photofluorographic or roentgenographic surveys be made only among tuberculin reactors.

The tuberculin skin test has assumed added significance today because of a demonstrated relationship between the size of reaction and clinical behavior: the larger the reaction in survey cases, the greater the risk of clinical tuberculosis (182). Cortisone may reduce tuberculin reactivity in tuberculosis and increase it in sarcoidosis (43)

It is important to read the skin reaction in millimeters of induration 48 hr. after 1, 5, 10, or 250 T.U. intracutaneously For screening purposes, the most reliable test is the 5 T.U. "intermediate" (0.0001 mg) dose of PPD. Only very rarely do persons proven to have clinical tuberculosis react only to 250 T.U. (second-strength PPD) or have no reaction at all (182).

[1] The survey of the literature pertaining to this review was completed in September, 1958.

[2] The following abbreviations will be used BCG (Bacillus Calmette Guerin); DHSM (dihydrostreptomycin); INH (isoniazid), IPPB (intermittent positive pressure breathing); PAS (*p*-aminosalicylic acid); PPD (purified protein derivative); SM [illegible]

of [illegible]

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be said to be contraindicated except in very seriously ill patients, and in persons with associated diffuse pulmonary emphysema, for fear of further loss of respiratory function (160).

A broad study of practices in the United States in 1954 revealed that 45 per cent of cases of active tuberculosis were not in a hospital. Many of the latter were still infectious (i.e., sputum-positive) when last tested, but the sputum status was unknown in most cases (25).

It has been thought that since rest seems to discourage multiplication of tubercle bacilli, and since INH acts *in vitro* only on actively multiplying organisms, rest may be contraindicated (215). This theory remains to be proven.

Streptomycin was discovered and first used to treat patients with pulmonary tuberculosis in 1944; it became generally available in 1946. Dihydrostreptomycin and streptoduocin—equal parts of SM and DHSM—were introduced later. *p*-Aminosalicylic acid was introduced soon thereafter and INH became generally available early in 1952. Present-day chemotherapy consists predominantly in regimens combining two or all of these three drugs. Little is known of the mode of action of the drugs. It is postulated that INH is absorbed by tubercle bacilli like an essential nutrient, only to interfere with one of its enzyme systems.

Viomycin, introduced in 1951, has a mild antimycobacterial effect but, because of potential hepatic and renal toxicity, must be given in rather ineffective doses twice weekly, rather than daily. Pyrazinamide alone is highly effective, but only for from four to six weeks (47). In patients who have never received either drug before, the regimen of pyrazinamide plus INH has been found to be highly effective (190). Oxytetracycline alone has a very mild antimycobacterial effect but seems, nevertheless, to be effective in combination with either SM or INH in delaying the emergence of bacterial resistance to these agents. Cycloserine has been available since 1955; it is quite effective in high (1 to 3 gm /day) dosage, but in this dosage causes toxic psychoses and epileptiform seizures (16). In the dosage that is usually safe (250 mg. twice daily), it is a relatively ineffective drug, alone or in combination (48). The dosage of antimycobacterial drugs and their major toxic effects are presented elsewhere in tabular form (160).

New drugs which have not yet been thoroughly studied include thioamide (205), streptovaricin (227), kanamycin (266), and thiocarbanidin (Thioban) (269).

The emergence of bacterial resistance to all antimycobacterial agents discovered so far has been demonstrated both *in vitro* and *in vivo* in man. Drug resistance probably occurs as a result of spontaneous mutations of originally susceptible bacterial cells. As an antimicrobial agent is brought into contact with populations of these organisms, the susceptible population is reduced while the resistant population tends to overgrow the others. The simultaneous use of two or more effective agents theoretically will improve the antimicrobial action because of the greatly reduced chance of spontane-

Depending on the medium used, the growth of typical tubercle bacilli requires from 4 to 12 weeks (136). In unusual circumstances a few true tubercle bacilli, particularly those obtained from patients after prolonged chemotherapy, may require up to 15 to 25 weeks for growth (34)

The pathogenic atypical or "anonymous" mycobacteria will grow on the various media in one-half the time or even less, required for typical tubercle bacilli (136). The colonies may be photochromogenic (i.e., develop a yellow color after exposure to light), scotochromogenic (i.e., develop a yellow color in the dark), or show the typical pale buff color of *Mycobacterium tuberculosis*. Morphologically, they may or may not be larger and more ovoid, but they may also be indistinguishable from it. The best methods, other than *considering growth characteristics, for identifying these atypical* bacteria are the absence of the neutral red reaction, absence of cord formation, reduced niacin content, primary INH, SM, and PAS resistance, especially the latter, and pathogenicity for mice but not for guinea pigs (54, 136).

The disease (mycobacteriosis) caused by these atypical bacteria is tentatively regarded as a form of tuberculosis, but may prove to be an entirely different disease (32). The organisms are mycobacteria, and the disease is pathologically and clinically quite indistinguishable from tuberculosis in both animals and man (54). Persons with this disease react to intracutaneous tuberculins prepared from the infecting organisms, they usually, but do not always, also react to ordinary PPD. The reaction to PPD is apt to be less than to the more specific antigens (71). The treatment of these infections is much the same as for ordinary tuberculosis. Very large doses of SM and INH are required because of the primary drug resistance. Pulmonary resection is well tolerated and effective (54).

The possibility of making a serologic diagnosis of active tuberculosis has been receiving considerable attention in recent years. While many have agreed that antibodies are formed against *M tuberculosis* in man, their reliable detection has eluded intensive search until recently. Using an agar double diffusion precipitation technique, an antigen prepared from virulent human tubercle bacilli seems to react visibly with antibodies only in cases of active tuberculosis (184)

During recent years it has become evident that rest therapy is less essential to the adequate treatment of pulmonary tuberculosis than formerly thought (267). In most cases of mild tuberculosis, rest in hospital, or even at home, is probably unnecessary except for indoctrination purposes The amount of rest indicated for advanced tuberculosis under modern chemotherapy has also been materially reduced, not only in quantity but in duration. *On the other hand*, rest is still effective and is indicated in the drug treatment failures, in those persons who harbor drug-resistant organisms, and in those who are not achieving much benefit from drugs or cannot be expected to do so (160). It is indicated also in those newly diagnosed cases in whom failure of chemotherapy may be anticipated. Strict bed rest may

for indefinite periods (22, 194). INH is the most generally accepted agent for prolonged chemotherapy because it is cheap, easy to take, relatively nontoxic, and theoretically may maintain the surviving parasites in a state of reduced pathogenicity and virulence for both the patient and his contacts

The best regimen for the treatment of serious pulmonary tuberculosis today is high-dosage combined SM and INH (160, 216). It is well to add PAS because of its ability in some patients to raise the serum concentrations of free, biologically active INH, in addition to its antimycobacterial effect (161). Pyridoxine (vitamin B_6) will prevent, but is slow to heal, peripheral neuritis due to INH. The dosage recommended is roughly 10 mg. for each 100 mg. of INH taken. Even in persons who seem to have failed to respond to therapy with SM, INH, and PAS, it is urged that high daily doses should be given a very thorough trial before changing to less effective regimens (160). INH-PAS is generally regarded as a very practical and effective two-drug regimen (154) Primary pyrazinamide-INH is also highly effective, but has the drawback of a very significant incidence of pyrazinamide hepatotoxicity.

Chemotherapy is indicated in all cases of active tuberculosis In addition, it is indicated in all infants who react to tuberculin and in recent converters up to the age of three or four, despite the absence of any other evidence of active tuberculosis. The use of chemotherapy in older, otherwise healthy children or adults with recent tuberculin conversion is probably harmless and may be helpful but is very apt to be unnecessary, except in circumstances of high exposure.

Corticosteroid therapy is capable of causing rapid and severe worsening of active, and even inactive, tuberculosis, but adverse effects do not by any means always occur (49) Brief corticosteroid therapy is safe to use while the patient is receiving an effective chemotherapy regimen. In overwhelming disease with great toxicity or after early failure to respond to chemotherapy, corticosteroids have proven very helpful (49)

The surgical resection of open cavities in patients who are still infectious —i e., the "open positive" lesion—while receiving a reliable chemotherapy regimen, is indicated except where the extent of the disease, age, or general condition of the patient, or pulmonary functional limitations contraindicate the procedure (22). Candidates for resection should have a previously unused or still effective drug or drugs available to cover the procedure, anticipated effectiveness is based not only upon the previous chemotherapy, but also upon current drug susceptibility tests Serious surgical complications are several times more frequent without good drug coverage than with it (164) Intervention with resection is usually not undertaken until near maximal benefits from chemotherapy have been achieved, this may require as little as three or four months or as much as 12 to 18 months (194). Provided the diseased area to be removed is confined to one or two lung segments, and no general surgical contraindications exist, intervention may be safely made early (i.e , after 1 to 2 months) during effective chemotherapy. Such early

ous mutation to multiple drug resistance (86). Clinical experience has confirmed this theory.

Testing methods for bacterial resistance *in vitro* and the relationship of these findings to clinical response to the drugs is somewhat controversial; a recent symposium on the subject is highly recommended (6).

If the majority of a population of tubercle bacilli isolated from a patient is found to show SM, viomycin, pyrazinamide, or PAS resistance *in vitro*, response to these drugs *in vivo* will be materially reduced or absent. In the case of INH the situation is complicated by an additional effect—a reduction in the virulence and pathogenicity for guinea pigs and for humans as well, especially in those which are highly resistant and "catalase-negative" (172). While final proof is still lacking, the continued administration of INH to such patients may be beneficial by preventing back mutation to INH susceptibility and, hence, to renewed virulence (215).

The risk of the emergence of clinical drug resistance is reduced not only by using multiple drug regimens, but also by avoiding interruptions in therapy (159) and by applying resection or collapse where feasible in order to achieve early reversal of infectiousness (160).

Provided the dosage is adequate, SM and INH have been shown to reach the lung, and particularly the tuberculous portions of lung, in effective concentrations. Apparently because of differences in rates of renal clearance of SM, dependent in turn upon renal function, SM serum concentrations vary between individuals (161) As a consequence, SM and DHSM toxicity are probably also related to the peak and duration of serum concentrations.

[illegible]

cally determined in man (160).

When high doses of INH and daily SM are used, these differences in serum concentrations of biologically active SM and INH probably have little clinical importance. When conventional or lower dosage is employed, as is practiced in many parts of the world, results may be anticipated to be less than optimal since some individuals will have less than optimal serum concentrations of these drugs (161).

In some patients, PAS is also inactivated excessively. This can be circumvented by intravenous administration. Correlation between serum concentrations of biologically active free PAS and clinical response to PAS treatment has not yet been demonstrated.

The duration of antimycobacterial chemotherapy should be no less than 12 months in any case, and for at least 9 to 12 months after reversal of infectiousness confirmed by repeated smears and cultures. In most cases of advanced tuberculosis, chemotherapy should be continued for from 18 to 24 months (160). In persons with persistence of "empty spaces," presumed to have been cavities from a review of serial films, including tomograms—i.e., the "open-negative" syndrome—, chemotherapy may well be indicated

wrapped in polyethylene sheets, or other substances, has proven to be a safe and effective substitute for standard thoracoplasty, despite the former high complication rate with intrapleural and extrapleural plombage (263). In patients past 60 years of age, the extraperiosteal plombage is usually left in permanently. In younger patients, some four to eight months after the initial stage, the plombage is usually removed, together with the overlying denuded ribs, thus converting the procedure into a conventional thoracoplasty. A resection may be performed at the second stage if the desired result has not been achieved (264). Plombage has the advantage of achieving a prompt thoracoplasty type of collapse, with little or no risk of paradoxical breathing or mediastinal flutter, which may be serious complications of conventional thoracoplasty in patients with very limited respiratory reserve.

The United States tuberculosis mortality rate seems to be levelling off, at least temporarily, at about eight deaths per 100,000 population per year. The new case rate has been slower in declining until recently, but the decline now seems to be gathering momentum; it is now approximately 40 new, active cases per 100,000 population per year. The risk of onset of clinical tuberculosis now rises rather steeply with advancing age, especially in males. The risk of clinical tuberculosis among tuberculin reactors remains very high in infancy (10 plus per 1000 reactors per year); a small peak is noted in the twenties, but the risk is low (one to two per 1000 reactors per year) from age 6 to 18 and again after 30 The risk rises again after 50, but reliable data on older persons are scarce. The excess morbidity and mortality we are now experiencing in the aged are believed to result from the heavy infection of "cohorts" (i e , persons born in the same year) of 10 to 30 years ago. As a consequence of these observations, a further steady decline in the new case rate is predicted for several years to come, unless some major disruption of our civilization occurs (78).

BCG vaccination is safe and effective. Because it does not give complete and lasting protection, and for other reasons well outlined elsewhere (9, 50, 183, 255), it is presently considered practical to confine the use of BCG to persons, families, or populations with a high risk of infection

Recent careful studies on the manner and risk of aerial dissemination of tubercle bacilli from hospitalized patients, and the reduction of such hazards by ultraviolet irradiation of hospital air, are worthy of very close scrutiny (204)

Bacterial Pneumonias

Staphylococcal infections are especially important in hospitals where drug-resistant organisms prevail. In one study, 12 of 189 staphylococcal infections appearing during hospitalization were pneumonias, with 8 deaths (268). Pneumonia tended to be bilateral, basal, patchy and, in severe cases, hemorrhagic or necrotic. Fulminating staphylococcal pneumonia may complicate Asian influenza and has a particularly gloomy prognosis in persons with chronic pulmonary disease. In infants and young children the disease

intervention may logically be undertaken when surgery can be anticipated ultimately to be necessary. In cases not suitable for resection, and where the cavity is superiorly and posteriorly located, collapse, either with standard thoracoplasty or with temporary or permanent extraperiosteal plombage thoracoplasty, should be seriously considered (264).

The advisability of resection of residual open spaces presumed to be cavities in persons who previously had tuberculous cavities in the same area, but whose sputum has been noninfectious for prolonged periods on chemotherapy—the "open negative" lesion— is now being re-examined. Until very recently it was felt that resection was mandatory in these cases because of the high rate of relapse (over 50 per cent) observed in such circumstances after prolonged original SM-PAS therapy (159, 194). On regimens including INH, however, relapse rates to date in persons with or without residual open lesions have been only five to eight per cent over a one- to three-year period after discharge from the hospital; however, very few of these patients had discontinued taking drugs (52).

The advisability of resection of "closed negative" lesions, nodules which may or may not have replaced an area of previous cavitation, continues to be controversial at this time. These solid lesions have been shown to be more likely to contain stainable and viable tubercle bacilli than are adjacent thin-walled open lesions; the latter not infrequently reveal "open healing" (34). On the other hand, three to five years' observation of persons who received 12 or more months of multiple primary chemotherapy has revealed no significant difference between those whose closed lesions were resected and those whose closed lesions were not resected (often because of too extensive disease) (194).

Resection may be indicated in cases of presumed pulmonary tuberculosis which have not been bacteriologically proven and where the diagnosis is in doubt.

Pneumothorax may be used under modern chemotherapy with a minimum of risk and a high degree of success in closing moderate-sized cavities (74, 106, 140). Where readily available, however, resection still appears preferable even in such cases.

Pneumoperitoneum was useful in achieving cavity closure in well-selected cases before chemotherapy and during the era of mildly effective chemotherapy. Used with highly effective (i.e., including INH) chemotherapy, pneumoperitoneum appears to be less effective than formerly in achieving cavity closure for reasons discussed elsewhere (160).

Before the advent of chemotherapy, standard thoracoplasty was clearly the most reliable form of treatment for chronic cavitary pulmonary tuberculosis (248). Provided the cavity is located in the upper lobe, and preferably posteriorly, thoracoplasty is still used with great benefit in patients who have failed to respond adequately to chemotherapy and who are not candidates for resection.

Extraperiosteal plombage thoracoplasty, using paraffin, lucite spheres

Respiratory infections caused by *Proteus vulgaris* or *Pseudomonas aeruginosa* are important causes of illness and death in poliomyelitis patients maintained in respirators Symptoms may be absent and physical signs, including fever, absent or hard to detect (26)

Brucellosis may cause circumscribed "caseous" nodules in the lungs (259); usually the only pulmonary manifestations to occur in the acute disease are occasional cough, expectoration, and chest pain (188).

The prophylactic use of antimicrobial agents and of corticosteroid hormones in infections has been a matter of debate. Antibiotic-treated comatose patients were compared with an untreated group; pneumonia was more common in the former (187). In nontuberculous respiratory infections, the corticosteroid hormones were beneficial only in vascular collapse (i.e., the Waterhouse-Friderichsen syndrome), when it occasionally occurs to complicate pneumococcal pneumonia, especially in elderly persons, or in those with complicating diseases, and in alcoholics (237).

Fungus Infections

An excellent symposium on all aspects of coccidioidomycosis was published in 1957 (8).[3] The disease is important not only because of the gravity of the problem, but also because of the diagnostic problems posed by its residual lesions, such as nodules or cavities, especially in persons living in nonendemic areas Exogenous reinfection and contagion are not problems, nor is dissemination after localization of the primary disease has occurred. A high index of suspicion is needed in making a diagnosis. The coccidioidin skin test may be negative, especially in the presence of severe disease. This should be followed by serial serologic studies, including those for histoplasmosis and blastomycosis. Cross reactions may occur. Precipitins appear early in the disease, but disappear after a few months. Complement-fixing antibodies are slower to appear and are always present in titers of 1:8 or higher in disseminated disease, whereas they may be absent in mild forms of the disease (232). Cultures of sputum or exudates should be handled extremely carefully to avoid infection of laboratory personnel by the mycelial form.

Despite its usual benignity, pulmonary coccidioma must frequently be removed for diagnosis, except in the endemic areas where its nature may be more clear. A residual cavity may be harmless but should be removed if repeated bleeding occurs, if it enlarges, if it is over 5 cm. in diameter, if it threatens to rupture into the pleural space, or if secondary infection occurs.

Amphotericin B, isolated from a *Streptomyces*, has shown considerable promise recently in the chemotherapy of the disease. It must be administered intravenously over many weeks' time and may cause fever, chills, phlebitis, and elevation of the blood urea nitrogen. Cases of disseminated disease have apparently been arrested by use of this drug (122).

[3] Ed note: see also Fiese, M. J, *Coccidioidomycosis* (Charles C Thomas, Springfield, Ill., 253 pp, 1958).

runs a rapid course with cough, fever, dyspnea, cyanosis, and collapse (19). Mortality is high and complications are common, especially empyema and pneumothorax (28). The respiratory tract may be the site of pseudomembranous changes similar to those occurring in the gastrointestinal tract *caused by staphylococci (233).*

Measures to prevent hospital-acquired infections have been proposed and include nose and throat cultures of hospital personnel, special care of blankets and linens, oiling of floors, and special techniques in operating *rooms and in caring for surgical patients (134). Oxygen humidifiers may* serve as sources of pathogenic bacteria (139). Primary staphylococcal pneumonia in adults runs a protracted course and is often complicated by abscess or empyema; however, the primary disease in previously healthy adults has a much better prognosis than in infants or persons already in a hospital with another illness (104).

Pneumonia in adults is usually caused by the pneumococcus Despite the fact that other chronic disease may be present in the elderly, the mor*tality is low if proper measures are initiated promptly (198). These should* include bacteriologic studies to detect the occasional pneumonia caused by organisms resistant to penicillin. The course is apt to be atypical in older persons. Bacteremia, leukopenia, and a history of alcoholism are poor prognostic signs. *The chest roentgenogram shows complete resolution within* three weeks in 80 per cent of cases (251). Tests on 114 strains of pneumococci showed no loss in their susceptibility to six major drugs over a period of several years (117).

Hemophilus influenzae pneumonia is uncommon; the organism more often causes croup or acute ulcerative bronchiolitis. Lobar, segmental, or patchy *involvement may occur in the pneumonic form (170).*

Despite antibiotics, acute pneumonia caused by *Klebsiella pneumoniae (Friedlander's) still has a high mortality, probably since it is common in* debilitated persons and in alcoholics Residual lung damage is frequent. Treatment should include SM in large doses plus one or two of the following. tetracycline, sulfadiazine (116), or chloramphenicol. If even suspected on *clinical grounds or from finding Gram-negative bacilli, treatment should not* be delayed

Tularemic pneumonia carried a high mortality prior to the advent of SM, which in 2 to 3 gm /day doses, is bactericidal Pleural effusion occurs in

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in diameter are seen radiographically; calcification and cavitation are rare. Lesions may be multiple and tend to locate in the lower lobes (128). Association with lymphomata may occur (84, 92).

Cryptococcus neoformans has been isolated from pigeon nests (119). Surgical excision of local cryptococcal pulmonary lesions is advocated. Amphotericin B and 2-hydroxystilbamidine have apparently arrested the disease in its meningitic form (131, 132).

Nocardiosis, caused by *Actinomyces asteroides*, is a disease of adults. The chest roentgenogram may suggest tuberculosis, abscess, metastatic tumor, or lobar pneumonia. The course is more acute than in tuberculosis, with a tendency to suppuration and dissemination. It should be suspected in pneumonias which do not respond to standard therapy and in cases of suspected tuberculosis in which partly or wholly acid-fast rods are seen (257, 258). Sulfadiazine is usually the drug of choice (258), but susceptibility tests and mouse protection studies may indicate the use of other antibiotics

Aspergilli are common contaminants of sputum but rarely may cause pulmonary disease, usually in debilitated persons (111). Cavitation may occur; a round density with a crescent-shaped radiolucent area at the superior pole, best seen by laminography, is said to be suggestive of the disease.

Mucor, or common bread mold, may, in debilitated persons, invade all parts of the lungs including the vessels, causing thrombosis and infarction. Spread of the disease may be by way of infected arteries The central nervous system and gastrointestinal tract may be involved (14).

Blastomyces dermatitidis has not been recovered from its natural habitat, but epidemiologic aspects suggest that it resides in the soil or soil products (38). Radiographically, North American blastomycosis may mimic pulmonary tuberculosis, but excessive pleural involvement and rib destruction may provide a clue to the true nature of the disease (105) Amphotericin B has effected arrests in the systemic form of the disease.

Other Infections

Progress in viral respiratory diseases has been reviewed recently (66, 238). Most respiratory illnesses are nonbacterial, noninfluenzal viral diseases Their classification suffers from a plethora of names for identical diseases, and because one virus, e g , influenza, may produce a variety of clinical syndromes.

The influenza pandemic of 1957 was especially serious in chronically ill persons. Bacterial invaders of the lung, such as pneumococci and staphylococci, played supporting roles (109). Streptococcal pneumonia and empyema were not uncommon during the epidemic. Indiscriminant use of antibiotics in influenza is discouraged (10).

Chickenpox pneumonia is a distinct entity usually occurring in young adults with severe cutaneous lesions (83, 125, 260). It may vary from radiographic manifestations alone to severe, massive, fulminating pneumonia with cough, chest pain, dyspnea, cyanosis, and death. Children with varicella

Histoplasmosis is much more common than was once believed. An excellent review is available (226). The roentgenographic classification includes arrested, benign active, acute disseminated, and chronic progressive (29). Local epidemics, including laboratory infections, have been reported (39, 80). Like other fungus diseases, histoplasmosis not infrequently complicates lymphomatous disease; in these instances its presence is often only discovered at autopsy (165).

Acute histoplasmosis is almost always benign and often goes undetected. The high incidence of reactors to histoplasmin in the Ohio and Mississippi River valleys is well known. Histoplasmosis primary complexes in the lungs often contain stainable organisms; furthermore, the larger the complex, the greater is the probability of finding histoplasmosis rather than tuberculosis. Splenic calcifications are commonly the result of histoplasmosis (243). Especially in the endemic area, solitary pulmonary nodules are commonly caused by histoplasmosis (30). The typical lesion is hard and rubbery, the gray center is surrounded by concentric laminations which cast a "calcific" shadow but are made up of fibrous tissue, sputum cultures for *Histoplasma capsulatum* are almost always negative as are those from resected material.

Difficulty in distinguishing between chronic tuberculosis and chronic progressive cavitary histoplasmosis has occurred (89). The disease causes multiple, bilateral, small cavities, as well as symptoms indistinguishable from those of tuberculosis. Bacteriologic and serologic tests may be the only means of differentiation. The cavitary form may remain stable or may result in death (245). Most, but not all, of these patients react to histoplasmin; more than two-thirds have significant titers of complement-fixing antibodies, and more than one-half yield positive cultures Significant titers (1:16 or higher) of complement-fixing antibodies usually indicate active disease, but may be present in apparently inactive cases (262), conversely, low titers may be seen in disease involving the adrenals (53) Superior vena caval obstruction (95) arising from fibrosing mediastinitis is an uncommon and serious complication and presents unusually difficult surgical problems. Fatal histoplasmosis frequently involves the adrenals.

In the cavitary form, despite lack of chemotherapeutic coverage, surgical resection has been successful (192). Treatment with amphotericin B shows considerable promise (130, 131). In severe cases, corticosteroids have been advocated to combat toxicity (82, 181), although this might theoretically predispose to dissemination in the absence of specific therapy.

Secondary infections with fungi appear to be increasing in number, possibly because of the greater use of antibiotics, nitrogen mustard, antimetabolites, and corticosteroid hormones (120). Moniliasis, aspergillosis, mucormycosis, and cryptococcosis have been described as occurring under one or more of these conditions (240, 247).

Pulmonary cryptococcosis is uncommon. Complicated by meningitis it is usually fatal without chemotherapy. When confined to the lung, symptoms may or may not be present. Circumscribed areas of consolidation 2 to 8 cm.

microbial therapy may be beneficial, as evidenced by reduction in cough, dyspnea, and sputum (218). Long-term tracheostomy in severe bronchiectasis has been employed with success (180). Use of detergents, mucolytic agents, and enzymes appears beneficial in the symptomatic treatment of these persons (44).

Two hundred and eight children under 15 with bronchiectasis were followed for an average of 6.4 years; over half-revealed clubbing; rales were often heard in the uninvolved lung. Collapse of lower or middle lobes was common. Severity of symptoms before operation, except for asthma, did not affect adversely the results of surgery, which were good, those with mild disease could be treated adequately without surgery. Resection prior to age eight had an increased morbidity (242). Studies on clubbing tend to show that precapillary bronchopulmonary artery anastomoses are associated (55).

Bronchiectasis may be more common in elderly people than is generally supposed; in 254 autopsies on persons over 70, bronchiectasis was present in 13 per cent; all had had symptoms and most revealed clubbing (5). Surgery in well-localized disease, especially where it is secondary to foreign body, is usually curative (51).

Bronchiectasis may occur in mucoviscidosis (also called "cystic fibrosis of the pancreas"), with or without evidence of pancreatic insufficiency (67). Cough, expectoration, and obstructive phenomena occur in the first year of life, with evidence of bronchiectasis later (126). The sweat test will reveal the excretion of abnormally large amounts of chloride in these patients (224). Salt depletion is a complication (197).

The mortality of well-treated lung abscess continues to fall, indicating better use of antibiotics. Drainage is now rarely necessary, having been replaced by resection when needed. Conservative treatment is usually successful (265). Frequent use of bronchoscopy as a therapeutic ally and to obtain secretions for bacteriologic study is important. The parenteral administration of pancreatic deoxyribonuclease in stubborn, slowly resolving abscesses has met with success (13).

After severe, nonpenetrating chest wall injuries, roentgenograms may show consolidation and a subsequent air-fluid level, despite the impression of lung abscess, rapid clearing usually occurs (99).

Mucoid impaction of the bronchi, a syndrome occurring chiefly in asthmatics and bronchitics, is characterized by rubbery plugs of mucus mainly in in second-order upper lobe bronchi (100, 103, 221); it causes episodes of dyspnea, cough, pain, and fever. Radiographic changes include segmental obstruction, abscess, pneumonia, and bronchiectasis. Medical treatment consist of fibrinolytic enzymes, IPPB, antibiotics, and bronchodilators. Surgical removal of involved lung may be necessary.

Diffuse Obstructive Pulmonary Emphysema

The cause of emphysema is not known. A recent series of papers presents an excellent description of the gross and microscopic pathology (146 to 152). The disease frequently accompanies pulmonary fibrosis from any cause, in-

appear to have secondary bacterial invaders, whereas adults have a hemorrhagic, mononuclear cell pneumonia with type A intranuclear inclusion bodies, a true viral pneumonia. The chest roentgenogram shows characteristic, widespread floccular densities, residuals of which may persist for several months. Physical signs in the chest may be minimal (83, 125, 260). A relationship between herpes zoster and varicella has been observed (83).

Transient radiographic changes may occur in children with pertussis or measles. Atelectasis is common in the former and enlarged hilar nodes in the latter (77).

Psittacosis may be protean in its manifestations (220); early use of the tetracycline drugs may suppress the development of specific antibodies (156).

Cat-scratch fever has been accompanied by pneumonia (222).

A well-known European disease, *Pneumocystis carinii* pneumonia, has been described in the United States (59). It occurs in premature and sickly infants and causes a 50 per cent mortality. Symptoms, signs, and roentgenograms are not diagnostic. The course is usually progressive. The etiologic agent is considered to be either a protozoon or a fungus that causes an interstitial plasma cell pneumonia with deposition of an acidophilic honeycombed material in the alveoli (24, 101). Agammaglobulinemia has been noted (24).

Echinococcosis is an important disease in Alaska and may be confused with tuberculoma or other round pulmonary lesions (61). Schistosomiasis, a common disease in Puerto Rico, may cause a pneumonic or miliary picture or present as cor pulmonale (bilharzial Ayerza's disease), because of an obliterative endarteritis following egg embolization of the lungs (64).

Bronchiectasis and Abscess

Accurate, complete mapping of the lungs prior to resection for bronchiectasis is important inasmuch as the filling of the basal segments, middle lobe, and lingula is often inadequate, and a small but significant number of cases have anterior segment disease (176). Combined tomobronchography may help in the detection and study of small localized areas of bronchiectasis, peripheral lesions, bronchial terminations, and distorted bronchial trees (91) A small area of bronchiectasis, particularly one containing inspissated material, may simulate tumor (219). The possibility of neoplasm underlying the lung abscess or chronic suppurative pneumonia should always be borne in mind. In persons with bronchiectasis or repeated pulmonary infections, agammaglobulinemia may be present (46), though most bronchiectatics show hypoalbuminemia and borderline hypergammaglobulinemia (253).

British authors have stressed the common finding of *H. influenzae* and sometimes *Diplococcus pneumoniae* in the purulent sputum of bronchitics and bronchiectatics. Treatment with a wide spectrum antibiotic plus a sulfonamide usually causes disappearance of *H. influenzae* and a change from purulent to mucoid sputum. Relapses are often associated with the reappearance of *H. influenzae* (3). American experience does not seem to reflect such a dominant role for that organism, but studies are scarce. Long-term anti-

The timed vital capacity and maximum mid-expiratory flow rate (133) provide reasonably simple and inexpensive tests for screening for early diagnostic or epidemiologic purposes. A thorough physiologic examination should include determinations of the maximum breathing capacity, lung volumes, mixing capacity (21), arterial blood studies and, finally, the diffusing capacity (40). The latter measurement is said to provide the best guide to prognosis (17).

In the fully developed disease therapy is symptomatic at best. Optimum results may be anticipated only in very early or mild cases in which further progression of the disease may be prevented by removal of all sources of air pollution, active control of respiratory infections (163), and possibly breathing exercises (229).

Because of the risk of increasing CO_2 retention and losing the hypoxic drive to breathe, it is best to use intermittent therapy or low concentrations of oxygen (i e , no more than 40 per cent, as with the nasal catheter) in emphysematous patients (81, 228). Therapy directed at heart failure is often surprisingly effective (93), its usefulness can only be determined by trial and error. The creation of a "fenestrated" permanent tracheostomy and teaching the patient to aspirate his own secretions have recently been advocated (143) Antimicrobial agents may be life saving. Their prophylactic use may have merit (75). Single, rather than multiple, drugs are preferred (118).

Surgical approaches to emphysema, such as the removal of blebs and invaginating pleural surfaces to reduce the size of the lung, and the removal of large solitary cysts or blebs to permit the expansion of more normal compressed lung, are rarely, not generally, applicable (102) All persons with a diagnosis of emphysema should be tried on various oral, inhalational, or rectal bronchodilators, corticosteroids have been recommended for a brief trial in all patients with a diagnosis of emphysema because of the possibility of a major bronchospastic element (23) Thyroid ablation with I^{131} probably should be reserved until all other treatment has failed (112).

Intermittent positive pressure breathing, widely used in the therapy of of this disease (15), seems basically unphysiologic since assistance in expiration, rather than overinflation on inspiration, is what these patients need (85) Nevertheless, IPPB provides an effective method for administering bronchodilator and wetting agents by inhalation. It is also best to use compressed air rather than oxygen in operating the apparatus because of the potential dangers of CO_2 retention (102).

Lung Cancer

The early detection of cancer of the lung continues to be a pressing problem. Retrospective roentgenographic studies show that some tumors were present for two or more years before symptoms were detected (203). Radiographic danger signals include unilateral hilar enlargement, unresolved pneumonia, thick-walled cavity, local obstructive emphysema, atelectasis, solitary enlarging nodules, and changes in the lumen of a bronchus (202).

cluding tuberculosis, silicosis, and bronchiectasis. In these disorders it may be diffuse but it is often localized and nondisabling. So-called "focal" or centrilobular, rather than diffuse, emphysema usually accompanies coal worker's pneumoconiosis in which an etiologic relationship seems to exist (185). An hereditary factor has not been excluded. The "bronchospastic" manifestations of the disease may be more a loss of elasticity than inflammatory mucosal swelling or muscle spasm (85), and may well be secondary rather than primary, especially since true emphysema is a relatively uncommon complication of true episodic chronic bronchial asthma (199). Industrial air pollution may be involved, as is suggested by epidemiologic studies in Great Britain (173). Sulfur dioxide, a common component of industrial gases, is capable of causing temporary paralysis of the tracheobronchial cilia (58), as well as increased airway resistance. Cigarette smoking plays at least an aggravating role (137), as appears to be true of other air pollutants (72). When kyphoscoliosis is complicated by cor pulmonale in adults (97), it is usually in association with emphysema (230).

The most generally accepted theory of the etiology of emphysema is that it occurs as a consequence of chronic, recurrent bronchiolitis and bronchitis, often centrilobular at the outset (147, 148, 149). Bronchiolar obstruction may or may not be found (127, 236). Its occurrence in men 10 to 20 times more frequently than in women suggests a hormonal factor (199). Observations in rats (79) and in man (153) suggest that damage to the cartilages of the tracheobronchial tree may increase the collapsibility of the airways on expiration and thus play an etiologic role. Premature aging, affecting particularly the elastic, collagenous, and reticular structures of the lung, is suggested by the characteristic loss of lung elasticity (37, 69). Emphysema may well prove to be a syndrome with numerous causes

Efforts to produce the disease in the experimental animal have so far been essentially unsuccessful (73). The disease seems to occur naturally in horses that eat moldy or dusty hay and is known as "the heaves" (2).

Emphysema is probably far more common than is generally realized. This is suggested by the frequency of cor pulmonale as a cause of congestive heart failure. Some hearts fail early and others do not fail at all in emphysema of apparently equal severity; this is tentatively explained on the basis of coexistent myocardial disease in those whose hearts have failed (7, 93). Especially in Great Britain, emphysema is often mingled statistically with "chronic bronchitis" (70).

Physiologically, the disease is characterized by interference with air flow, particularly on expiration, with marked loss of ventilatory capacity, interference with mixing of gases in the pulmonary air spaces, and reduction in the transport of oxygen into the capillary blood (85). Reduction in the size of the pulmonary vascular bed, increased pulmonary vascular resistance, pulmonary hypertension, chronic cor pulmonale, and cardiac failure are common complications (200). An excellent symposium on the pulmonary circulation and respiratory function is highly recommended (7).

is the prognosis (167). Probably less than one-third of persons with the diagnosis have "resectable" or potentially curable lesions (88, 94, 171, 177, 201, 256). Five-year "cures" in those in whom a "curative" resection has been performed range from 20 to 30 per cent. Lobectomy may be curative for carcinoma at times, especially in solitary nodular or localized alveolar cell carcinoma; lobectomy is preferable in persons with low pulmonary reserve. "Radical" pneumonectomy, with resection of involved hilar nodes, is preferred to lobectomy or pneumonectomy by some surgeons (177).

Even in tumors discovered accidentally by survey roentgenograms, the the five-year cure rate may be disappointing (168). The five-year survival rate of resected solitary nodular cancers may reach 75 per cent (60). The five-year survival rate correlated well with microscopic evidence of the absence of blood vessel involvement in the resected specimen (45).

Radioactive colloidal gold or chromic phosphate will prevent reaccumulation of fluid for prolonged periods in 50 per cent of subjects with malignant pleural disease without bulky metastases (36, 114, 175). Nitrogen mustard often has outstanding palliative effect in anaplastic carcinoma, malignant effusions, and superior vena caval obstruction caused by tumor (213). "Curative" radiation therapy has been followed by five-year survival in 11 of 33 selected, proven cases of lung cancer given 4000 to 5000 r (231).

In 60 cases of bronchial adenoma, dry cough, unilateral wheeze, and recurrent hemoptysis were common. Symptoms were often present for years before the diagnosis was made. The chest roentgenogram is not characteristic. Metastasis occurred in 15 per cent. Wide excision was usually curative (179).

Sarcoidosis

It is commonly believed that sarcoidosis is a collection of clinical syndromes with a more or less characteristic pathologic picture and probably more than one etiology[4] (57). Recently, pine pollen has been added to the

[4] "Sarcoidosis is a systemic disease, or group of diseases, of undetermined etiology and patho[illegible]

[illegible] Clinically, the disease most commonly involves lymph nodes, lungs, skin, eyes, liver, spleen and phalangeal bones. The course is usually chronic and constitutional symptoms vary markedly. More specific symptoms, when present, relate to the tissues and organs involved.

"The intracutaneous tuberculin test is frequently negative, but a positive test does not [illegible]

an [illegible]

are [illegible]

with a compatible histological picture, provided beryllium poisoning and known infectious processes can be excluded.

Bronchography may aid in the diagnosis of peripheral carcinomas; cytological studies are of little help (206). Previous roentgenograms may be very helpful although the absence of change over several years does not assure benignity. The presence of calcium is not a reliable sign of benignity, unless the lesion is completely calcified or shows a laminated or "popcorn" type of calcification (60, 174).

Differentiation between pneumonia and carcinoma with pneumonia may be difficult. Pneumonic consolidations behind cancerous obstruction are apt to be associated with insidious onset, excessive cough, difficult expectoration, weight loss and hemoptysis (121, 223). Alcoholics, on the other hand, are likely to show slow resolution of classical right upper lobar pneumonia simulating cancer (121).

Cytologic diagnosis of bronchial cancer may be highly successful (250). Best results are obtained in tumors of the main and lower lobe bronchi, in the squamous cell and adenocarcinomatous types. The chief cause of false negative tests is bronchostenosis or apparent failure of a peripheral lesion to communicate with a bronchus (249). Sputum is a better source of cells than are bronchial washings (209). In cases with positive cytology, those with visible lesions have a poorer prognosis than do persons whose lesions are not seen by bronchoscopy (108). Midlung tumor, beyond bronchoscopic vision, has a higher rate of resectability than do tumors in other locations (27).

Scalene node biopsy may be diagnostic of metastasis from the lung; sqamous cell carcinoma is rarely found, however. Evidence of metastasis to this group of nodes is considered a contraindication to curative surgery, although tests of the validity of this assumption are still under way (178).

Angiocardiography (4, 138) and phlebography (42) of the superior vena cava have been used in the evaluation of lung and mediastinal lesions, especially with regard to vascular compression or invasion. Decision as to the ability of the patient to tolerate pulmonary resection in various types of lung disease may be aided by measurement of cardiopulmonary function during balloon occlusion of the pulmonary artery or during cardiac catheterization (166).

Brain metastases are common in bronchial cancer, especially with adenocarcinoma and the undifferentiated type (90). Eosinophilia suggests metastasis (141). It is estimated that 40 per cent of the lung metastases discovered at autopsy are missed by chest roentgenogram (129). Lymphangitic carcinomatosis from cancer of the stomach, lung, breast, or pancreas presents a distinct syndrome of dyspnea, cough, cyanosis, and sometimes heart failure. The chest roentgenogram shows miliary mottling, reticulation and large hilar shadows (18). Metastases to bone are from bronchial carcinomas in 20 to 30 per cent of cases (157). In persons whose primary tumor has been successfully removed, favorable results have been obtained in the resection of metastases to the lungs, especially sarcomas (96, 244).

The younger the patient with cancer of the lung, the more unfavorable

(142). These disturbances may be precipitated by high vitamin D treatment or sunlight. Increased calcium absorption has been tentatively incriminated, but the urinary excretion of calcium is greater than can be explained by increased absorption. Corticosteroid therapy usually reduces the hypercalciuria (115, 124); also helpful are a low calcium and low vitamin D diet (174); sodium phytate—inositol hexaphosphoric acid—combines with calcium to form an insoluble salt and thus will increase calcium excretion in the feces (107).

Three types of pulmonary physiological disturbances are described in pulmonary sarcoidosis, the first two usually associated with radiological evidence of pulmonary fibrosis. (*a*) reduced lung volume with impaired gas diffusion; (*b*) reduced lung volume with hyperventilation; and (*c*) diffuse obstructive emphysema, usually with only slight evidence of fibrosis (145).

The diagnosis of sarcoidosis is aided by finding hyperglobulinemia in about two-thirds of cases, usually associated with hyperproteinemia (113). A positive Kveim test is reported in from 50 to 90 per cent of cases proven by other means False positive Kveim tests seem not to occur (196).

It is now generally agreed that corticosteroid therapy is helpful in sarcoidosis provided it is given before extensive pulmonary fibrosis has occurred (113, 115, 124). Relapse of pulmonary sarcoidosis is often noted when corticosteroid therapy is stopped INH prophylaxis against tuberculosis is urged during corticosteroid therapy for sarcoidosis, especially in those who react to tuberculin.

The prognosis of sarcoidosis is less favorable than is generally realized It is ultimately fatal in from 5 to 50 per cent (35, 113, 135, 169, 225). The usual cause of death is right heart failure secondary to pulmonary fibrosis Fatal hemoptysis may occur. Tuberculosis is reported to cause death in from 1 to 13 per cent. Permanent respiratory disability is reported in from 25 to 30 per cent. Pulmonary sarcoidosis is more apt to become chronic than are the purely extrapulmonary forms (169, 225) Persons with a diffuse miliary (shadows of less than 1 mm in diameter) pulmonary involvement seem to have a more favorable long-term prognosis than those with nodules of 3 to 5 mm and than those with radiological evidence of fibrosis The presence and degree of lymph node involvement appears to have little influence on prognosis (135)

Collagen Diseases

Polyarteritis not infrequently involves the lungs, and if so, is apt to involve them prior to other systems. Respiratory symptoms may be pneumonic, bronchitic, or asthmatic; marked eosinophilia is noted in about 50 per cent. Some have nasal or middle ear granulomata The bronchitic illness is usually quite severe. In the asthmatic syndrome the onset is late in life in contrast to true asthma, the family history is apt to be negative for allergies, and a long time lag may occur between the onset of asthma and the other symptoms of polyarteritis. The chest roentgenogram may simu-

list of possible etiologic agents, on the basis of a vaguely similar distribution of pine forests and the epidemiologic distribution of the disease. Pine pollen also contains an acid-fast material and evokes a granulomatous reaction when injected into the experimental animal (56).

Despite numerous arguments to the contrary, tuberculosis is presently no longer widely believed to be one of the common causes of the syndrome (76, 195). Only about 20 to 30 per cent of patients with proven sarcoidosis react to tuberculin. Tuberculin conversion in a patient with sarcoidosis may herald the onset of one of its most common and serious complications (76). On the other hand, some patients with proven tuberculosis have lost their tuberculin reactivity when sarcoidosis has occurred as a complication (239). It has been suggested that the frequent association of sarcoidosis with tuberculosis may be related to prolonged and unwarranted stays in tuberculosis sanatoriums (57).

Sarcoidosis is most common in Negro females between 20 and 30 years of age in rural areas. Epidemiologically, the disease is reported to be prevalent in rural areas, especially in the southeastern United States, and more recently in the northeast and north central states (57) Sarcoidosis often shows improvement during pregnancy, with a tendency to exacerbation following delivery (144).

Hepatic biopsies generally reveal sarcoidosis to be periportal, with a tendency to a more diffuse involvement in tuberculosis, biopsy of lung or lymph node is preferable to liver, in which many other sarcoid-like lesions are apt to be found. Skeletal muscle biopsy may be useful (189, 254). Frequently, involvement of the myocardium, lacrimal and parotid glands, skin, and uveal tract tend to differentiate sarcoidosis from tuberculosis (113) Sarcoidosis may involve the pleura, peritoneum, pericardium, and nervous system, but not commonly (115). Extrapulmonary sarcoidosis occurs much more commonly in Negroes than in the white races (225).

Clinically, the frequency of organ involvement reported in the literature (113, 115) is as follows:

Lymph nodes, 37–100%	Spleen, 18–40%
Lung, 40–80%	Uveal tract, 20–30%
Hilar lymph nodes, 72%	Parotid glands, 4–10%
Skin, 25–40% (including erythema nodosum in 1–10%)	

Hypercalcemia, hypercalciuria, and elevated alkaline phosphatase are reported in sarcoidosis in from 5 to 10 per cent (68, 107, 124). Nephrocalcinosis and renal functional impairment may ensue. Bone changes are very uncommon and are essentially never found in the predominantly pulmonary form

"Spontaneous clinical recovery, with or without recognizable fibrosis, may result, or sarcoidosis may persist for years with varying functional alteration of the tissues [illegible] ending fatally."— [illegible] National

Two acute diseases seen in welders are "metal fume fever," a febrile illness with dry cough, chills, cramps, headache, and nausea, caused by inhalation of zinc oxide fumes (208, 246), and "ozone poisoning," which may cause an illness whose symptoms mimic myocardial infarction, pulmonary embolism, or severe pneumonia (123)

Radiation fibrosis of the lungs may result in secondary bronchiectasis or alveolar capillary block (241). Cortisone given during radiation therapy does not appear to prevent its occurrence (41). On the other hand, diffuse interstitial pulmonary fibrosis (the Hamman-Rich syndrome) appears to respond to corticosteroid hormones in some instances (191).

Pulmonary alveolar microlithiasis is usually discovered on routine chest roentgenogram. Symptoms may be absent, but eventually pulmonary insufficiency may occur The radiographic appearance is pathognomonic: fine, sand-like, bilateral mottling, especially at the bases, the individual granular, sharp lesions being less than 1 mm in diameter. The lungs are heavy and gritty. Laminated calcium deposits are found in the alveoli Etiology is unknown and treatment is unavailable (234).

Primary systemic amyloidosis commonly causes cardio-pulmonary signs and symptoms. Lung involvement occurs in one-third of cases and includes blood vessel lesions, pleural thickening, and alveolar wall infiltration. Cor pulmonale may supervene (214)

Symptoms and signs suggesting brain tumor may be manifestations of pulmonary insufficiency (12) Conversely, dyspnea may be an initial complaint of persons with muscular atrophy, amyotrophic lateral sclerosis (158), or cerebellar ataxia (110).

Significant numbers of persons with esophageal disorders have chronic pulmonary abnormalities, probably secondary to aspiration pneumonitis (252).

Pulmonary alveolar proteinosis is a newly-described disease which resembles *Pneumocystis carinii* infection morphologically, but occurs in adults. The radiographic appearance is that of pulmonary edema without, however, symptoms indicative of this syndrome Clinical symptoms are often less than would be expected from the roentgenographic appearance, especially at the outset The course is chronic and may be fatal The name is derived from the proteinaceous material that fills the alveoli. The disease defies diagnosis except by pulmonary biopsy (212).

late tuberculosis, including cavitation; local or diffuse, soft, near-miliary-sized lesions, transient infiltrates, and pneumonic consolidation, with or without effusion, have been described (210, 211). Hilar nodes are frequently enlarged and, in severe cases, especially with renal involvement, the infiltration has the so-called "bat's wing" distribution (207). A related entity, Wegener's granulomatosis, is characterized by necrotizing granulomas of the upper or lower air passages, with necrotizing vasculitis and focal glomerulitis Pulmonary lesions are usually discrete and may cavitate (207). These may show remission on treatment with corticosteroid hormones

Nonspecific changes are common during the course of disseminated lupus erythematosus and include pleural effusion, pneumonia, bronchitis, pulmonary hemorrhage, and edema (162). Pulmonary arteries and arterioles may be the site of degenerative and fibrous changes (1).

In rheumatoid arthritis widespread mottling may be seen in the chest roentgenogram, these changes are associated with inflammatory changes in the arteries and bronchioles (193). Multiple, rounded densities in the lungs of coal workers with rheumatoid arthritis are widely recognized as Caplan's syndrome.

Alveolar cell carcinoma may occur in a setting of chronic inflammation or fibrosis (including scleroderma) or both (20, 235)

Eosinophilic granuloma of the lung is a relatively benign disease characterized by diffuse pulmonary infiltrates which may resemble polyarteritis in certain respects (11)

Miscellaneous

The lungs of persons dying of malignant hypertension and receiving hexamethonium bromide may exhibit a fibrinous, noninfections pneumonitis (186).

The now well-known "Pickwickian" syndrome (33) consists of extreme obesity, somnolence, cyanosis, Cheyne-Stokes respirations, polycythemia, and cor pulmonale. It has been attributed to marked obesity causing alveolar hypoventilation, which is reversible if weight reduction occurs True pulmonary disease is not a necessary part of the picture.

Idiopathic pulmonary hemosiderosis may rarely affect young adults, causing cough, hemoptysis, anemia, dyspnea, cyanosis, a reticulated radiographic pattern, and eventual death due to heart failure or pulmonary insufficiency (31)

Farmer's Lung, a disease first described in England in 1932, follows exposure to moldy hay, it is characterized by cough, dyspnea, fever, chills, and weight loss (65, 87) Repeated exposure may lead to recurrences Chest roentgenograms show nonspecific infiltrates. Lung biopsy demonstrates a granulomatous interstitial pneumonitis with epithelioid and giant cells (65). The process is not to be confused with Silo-Filler's Disease, a diffuse chemical pneumonitis caused by exposure to nitrogen dioxide, which may accumulate in toxic amounts in silos (62, 98).

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great variety of overt, insidious, and inadequately explored hazards to human health and life. Whether these hazards arise with the discharge of huge tonnages of industrial wastes upon the soil, into the streams, or into the atmosphere of the earth, or whether they derive from the harnessing of power or from the handling of the products of industry, many of them are new to the human environment and, hence, to medical and hygienic experience, in that the human organism has not encountered them previously or it has done so only briefly or at a very low [illegible]

[illegible] in May of 1958, recommended by the Study Section for Sanitary Engineering and Occupational Health, and called by the National Institute of Health. The publication of six of the papers (1) of this conference in abbreviated form in *Public Health Reports*, in lieu of proceedings, will provide background information, especially in relation to the need for research. A much more elaborate source book which does not deal with the subject matter from the viewpoint of preventive medicine, but concerns itself with basic changes wrought by man in the earth's environment, is the recorded result of an international symposium held in Princeton, New Jersey, in 1955, in which 70 experts in various fields of knowledge assembled from many countries for a discussion of "Man's Role in Changing the Face of the Earth" (2).

In view of the scope and variety of the human environment in times past and present, and its inevitable effects upon man, the following paragraphs may seem but a meager representation of the progress of medicine toward the understanding of these effects Be that as it may, the present problems of environmental health which present the greatest need, as well as the greatest opportunity, for progress are those which flow from industry and from the influence of industrial operations upon the population within both industry and the larger community. This is not to suggest that there are no significant omissions of subject matter from this review or that the coverage of matters included is adequate, but it may be hoped that the attention of the reader, whether casual or in urgent need, will be directed by the discussion into the main channels and by other references into the byways of the subject.

SPECIALIZED KNOWLEDGE AND PROFESSIONAL TRAINING

Effective professional practice in the field of environmental medicine in an industrial society demands the acquisition of a large body of specialized knowledge and technical skill which, until recently, has had but slight cultivation in American educational institutions and professional circles. It seems likely that the most significant features of the progress of environmental medicine to be noted within the past three decades have culminated, in 1956 and 1957, in several closely related and important developments. An outstanding symbol of these developments was the formal recognition in

ENVIRONMENTAL MEDICINE[1]

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Any attempt made at this time to bring together the current contributions to the field of environmental medicine to assemble and appraise the recently acquired knowledge which implements the practice of medicine as the latter derives from the direct impact of the modern environment upon the illnesses and disabilities of humankind alone or even to cite the sources of information for those who would examine more closely the subject matter

ler this heading is doomed to be

both to the author of any such

ɔ it for guidance in their thinking

or in the performance of their professional duties Indeed so poorly has this field been defined that there is no periodical in professional and scientific literature which purports or undertakes to delineate its major features d sciplines and techniques To add to the difficulty the scope of the field is so broad as to extend into almost every general and specialized field of medical and hygienic practice training and research

In effect the role of medicine whether through the efforts of the phy s cian alone or in combination with those of the many scientists engineers and other participants in the daily work of the health profess ons is largely that of protecting mankind aga nst the threats that lurk in his environment or of succoring him or comforting him when he comes to grief under their impact

The modern environment in so far as it differs from that wh ch hitherto has challenged the knowledge and the technical skill of the physician and hygienist is composed in large part of factors created by the application of the ph

from the aspect of hazard and stress are speed of movement on our part and all around us such as has never been seen or dreamed of in prior time There is a relentless demand for alertness skill and judgment there are machines in every direction which have multiplied manpower and taken over much of the burden of human labor but with an accompaniment of strident noise and harsh vibration and the ever present danger of unleashed destructive forces Above all there is a veritable Pandora s box of new and old chemi cals wh ch along with a multitude of industrial processes have created a

[1] The survey of l terature pertain ng to this review was completed n October 1958

great variety of overt, insidious, and inadequately explored hazards to human health and life. Whether these hazards arise with the discharge of huge tonnages of industrial wastes upon the soil, into the streams, or into the atmosphere of the earth, or whether they derive from the harnessing of power or from the handling of the products of industry, many of them are new to the human environment and, hence, to medical and hygienic experience, in that the human organism has not encountered them previously or it has done so only briefly or at a very low order of intensity. These features of the modern environment, and others that are related to them, were explored and portrayed in a conference on "Man Versus Environment," in Washington, D. C., in May of 1958, recommended by the Study Section for Sanitary Engineering and Occupational Health, and called by the National Institute of Health. The publication of six of the papers (1) of this conference in abbreviated form in *Public Health Reports*, in lieu of proceedings, will provide background information, especially in relation to the need for research. A much more elaborate source book which does not deal with the subject matter from the viewpoint of preventive medicine, but concerns itself with basic changes wrought by man in the earth's environment, is the recorded result of an international symposium held in Princeton, New Jersey, in 1955, in which 70 experts in various fields of knowledge assembled from many countries for a discussion of "Man's Role in Changing the Face of the Earth" (2).

In view of the scope and variety of the human environment in times past and present, and its inevitable effects upon man, the following paragraphs may seem but a meager representation of the progress of medicine toward the understanding of these effects Be that as it may, the present problems of environmental health which present the greatest need, as well as the greatest opportunity, for progress are those which flow from industry and from the influence of industrial operations upon the population within both industry and the larger community. This is not to suggest that there are no significant omissions of subject matter from this review or that the coverage of matters included is adequate, but it may be hoped that the attention of the reader, whether casual or in urgent need, will be directed by the discussion into the main channels and by other references into the byways of the subject.

SPECIALIZED KNOWLEDGE AND PROFESSIONAL TRAINING

Effective professional practice in the field of environmental medicine in an industrial society demands the acquisition of a large body of specialized knowledge and technical skill which, until recently, has had but slight cultivation in American educational institutions and professional circles It seems likely that the most significant features of the progress of environmental medicine to be noted within the past three decades have culminated, in 1956 and 1957, in several closely related and important developments. An outstanding symbol of these developments was the formal recognition in

A reflection of the increase in interest in noise-induced deafness is the rapidly expanding volume of published material that has appeared within a few years. A textbook by Sataloff (25) and a monograph by Glorig (26) offer comprehensive presentations of the subject. The American Industrial Hygiene Association has recently published an *Industrial Noise Manual* (27) aimed primarily at the needs of the industrial hygienist. *Noise Control*, a bimonthly publication of the Acoustical Society of America, has been published continuously since 1955. In addition to the publications described, a regular summer course in industrial deafness is offered at Colby College, under the direction of Sataloff & Hill (28).

Since the classic work of Kryter (29), attempts have been made to establish rational criteria for the risk of deafness. Parrack (30) has presented a comprehensive discussion of the auditory and nonauditory effects of levels of sound characterized by high energy The American Standards Association organized the Exploratory Subcommittee Z24-X-2, and the report of this group (31) provides valuable information A review of this material by Rudmose (32) indicated that no fixed criteria for the appraisal of the risk of deafness could be set. Glorig (33) has suggested the following interim criteria in the light of currently available information.

If the sound energy of the noise is distributed more or less evenly throughout the eight octave bands, and if a person is to be exposed to this noise regularly for many hours a day, five days a week, for many years, then if the noise level in either the 300–600 band or the 600–1200 band is 85 db (or higher), the initiation of noise exposure control and tests of hearing is advisable

Retrospective studies of the relationship of loss of hearing within specific industrial populations to exposure to noise on the part of these populations have appeared recently. Rosenwinkel & Stewart (34) have found a significantly greater permanent loss of hearing among persons who have been exposed for long periods to sustained noise at 80 decibels than that which occurred within a similar population following prolonged exposure to noise in an office. Grings, Summerfield & Glorig (35) reviewed the experience of the employees in an aircraft industry They stressed the difficulties encounter[illegible] to determine relationships between

[illegible] ...al loss of hearing caused by industrial noise has been awarded in some of our states Fox (36) has presented the approach to this problem and the resultant experience in Wisconsin, Symons (37) has reported the developments in New York State, Washburn (38) has described the situation in California, and Symons (39) has summarized the status of the matter in Pennsylvania, Missouri, New Jersey, Kentucky, and Minnesota. Davis (40) has discussed the problem of assessing auditory disability.

With growing awareness of the problem, descriptions of programs for the conservation of hearing have appeared with increasing frequency. Most

The literature relating to the etiology and pathogenesis of silicosis is voluminous, but the mechanism by which silica stimulates fibrogenic cells to produce collagen at an abnormal rate is not yet understood. Davies (11) reviewed the literature on the physics and chemistry of dusts with respect to the development of silicosis and pneumoconiosis. Since then, various reports have dealt with the silica-solubility theory, immunological considerations, the fibrogenic activity of various types or forms of silica dust, and the treatment of experimentally produced silicosis (12 to 19).

The pathology and the disability produced by either bituminous or anthracitic coal dusts have become topics of increasing importance and interest. In coal workers' pneumoconiosis, the pathology and pathogenesis differ distinctly from those of classical silicosis (20, 21). Two forms of the disease have been described, the macular or simple, and the complicated or massive form. The lungs, in the simple form, contain, characteristically, numerous small aggregations of dust, 1 to 2 mm. in diameter, located near the divisions of the bronchioles and the adjacent arterioles. The dust, contained mostly in phagocytes, may be seen partly in the interstitial tissue, in the alveoli, and in the alveolar walls. Within the aggregates of dust, there is a fine mesh of reticular fibers, and focal emphysema is prominent in the surrounding areas In the massive type, coarse, hyalinized collagen fibers are seen, but the characteristic whorls of silicosis are not present. Small foci of lymphocytic chronic inflammatory cells and dust particles or clumps of such particles are seen within the lesions Necrosis, caseation, and cavitation of either the infective or ischemic type are found occasionally, and suggestive evidence of tuberculosis has been noted in some specimens

The diagnosis of coal workers' pneumoconiosis is made primarily from an occupational history of exposure to coal dust and the finding of changes, on chest x-ray films, which are compatible with the effects of exposure to the dust. An international radiological classification of pneumoconiosis has been reviewed by Fletcher (22), and standardized chest films illustrating the various categories in this classification are now available (23). In view of the mounting abundance of evidence to indicate that coal dust is capable of producing disabling pulmonary disease, Kammer (24) has cited the need for a critical reassessment of the still widely held American viewpoint that occupational pulmonary disability from exposure to dusts in the bituminous coal industry can result only from silicosis.

Noise and Auditory Impairment

In recent years, auditory impairment in consequence of noise has emerged as one of the significant hazards of the industrial environment. Occupational loss of hearing is not new, as one recalls the phenomenon of boilermakers' deafness and other examples of industrial deafness known to previous generations. Modern developments, such as those in the aircraft industry, have increased both the intensity of noise and the numbers of persons exposed to noises of high intensity.

the gonadal dose of radiation in order to mitigate genetic effects. The report of the National Research Council of the National Academy of Sciences in 1956 emphasized the need for reducing the gonadal dose but did not overlook the further advisability of reducing total body radiation. With this report at hand, the National Committee on Radiation Protection and Measurement (NCRPM), early in 1957, lowered the maximum permissible level of exposure. While retaining the earlier limitation of 0.3 rem per week for whole body radiation under occupational conditions, the Committee reduced the maximum yearly dosage to 5 rems, thus, in effect, reducing the weekly limit to 0.1 rem. Other extensive changes were made in the maximum permissible limits, with the primary purpose of reducing the gonadal radiation of the entire population to a minimum The details of these changes can be obtained from the National Bureau of Standards, or through their publication in the relevant journals (58).

Renewed interest in the reduction of occupational exposure to ionizing radiation (including that incurred by physicians and other professional personnel) has led to a plethora of articles on the details of methods for so doing A succinct statement of the principles involved may be found in an article by Ardran (59). The matter is presented in its proper perspective by Spiers (60) in a published address.

Whole-body radiation counters are now in use in several installations in the United States Their availability furnishes an instrument for the determination of extremely minute levels of radioactivity and may settle questions which formerly have been answerable only with the greatest difficulty, or not at all, concerning the body burden of radiation materials

The article by Saenger and co-workers (61) on procedures in dealing with accidents with radioactive materials has been adopted in larger part by the National Committee on Radiation Protection and Measurement, and should be accessible to anyone interested in environmental medicine. Saenger has described in detail the immediate and later steps which should be taken when radioactive isotopes are spilled, and although these were recommended in 1952, they have not been superseded The Atomic Energy Commission now maintains emergency teams in various sections of the country, and these are available to provide advice and assistance in dealing with accidents involving radioactive materials

Effects of Microwaves

During the past few years the question of the effects of microwaves on biological systems, and particularly on human beings, has assumed increasing importance. Knauf (62) has reported some of the preliminary results of recent investigations of such effects At the present time the maximum safe level of exposure to microwaves has been established by the United States Air Force at 0 01 watt per sq. cm. A comprehensive program of investigation is now under way to determine the suitability of this standard of safety. The equipment in use today is not of greatest concern to the Air Force,

comprehensive of the published programs is that of the Subcommittee on Noise in Industry of the American Academy of Ophthalmology and Otolaryngology (41). Together with a card for recording relevant data, as developed by the same group (42), this constitutes a master guide which may be adapted to the needs of specific industries. In general, programs for the conservation of hearing include the following activities: (*a*) assessment of the hazard by means of surveys of the environment; (*b*) collection of baseline and periodic audiograms from exposed personnel; (*c*) clinical appraisal of personnel with significant hearing loss and selective placement of such personnel, (*d*) reduction of intensity and duration of exposure to noise by engineering methods when feasible; (*e*) use of proper personal protective equipment when the hazard cannot be controlled otherwise; and (*f*) educational efforts aimed at implementing the activities enumerated above.

Scholtz (43) has pointed out the role of the industrial hygiene engineer in a program for the conservation of hearing. He has described the techniques of the environmental survey and indicated the availability of consulting services for the abatement of noise. Peterson (44) has described a new impact noise meter for industrial use. Poth & Weinberg (45) have presented the concept of the duration of exposure as a means of expressing tolerable exposure to noise of high intensity in terms of time.

The principles of audiometry, as a technique of monitoring, have been discussed by Davis, Hoople & Parrack (46). Along with Summerfield, Glorig & Wheeler (47), they are of the opinion that there is now no suitable test of susceptibility to noise-induced hearing loss. Glorig & House (48) have advanced the concept of single-frequency audiometric screening as a method for the periodic evaluation of the hearing status of an industrial population. Automatic audiometry has become available, and the instruments of Rudmose and Brogan have been described (49, 50, 51). The choice of a proper environment for industrial audiometry has been discussed by Wheeler (52). Fox (53) has described the role of the consulting otologist in a program for the conservation of hearing, with specific reference to the clinical appraisal of persons who have sustained significant impairment.

The use and usefulness of both plug and muff types of ear defenders have been described. Glorig (54) has appraised the extent of the protection provided by ear plugs, Wadsworth (55) has described the state of development of a specific muff type of ear protectors, and Von Gierke (56) has reviewed the extent of the attenuation of noise by both plugs and muffs Wheeler & Glorig (57) have discussed the problems encountered in establishing a program involving the use of personal protective equipment in industry.

Radiation Hazards

The techniques for the control of hazards of nuclear radiation have advanced in many directions Several of these are of special interest and value in their applications to environmental medicine.

Recent emphasis has been directed increasingly toward the reduction of

insecticides for specific uses have not been outstandingly successful. On the other hand, the requirements with respect to toxicological information, prior to the introduction of new insecticides, are increasing steadily. There are both advantages and disadvantages in this situation, but they add to the impetus toward the discovery of safe yet effective agents.

From the aspects of medical therapy, a noteworthy development has been the recent introduction of certain oximes and hydroximes containing the ionizable NO-H linkage. These appear to be capable of reactivating cholinesterase and hence are of importance in the therapy of intoxication induced by the organic phosphorus insecticides. Childs and his associates (63) have reported their observations and have indicated also that some oximes exert an inhibitory effect of their own on cholinesterase.

Holmes & Robins (64) found that pyridine-2-aldoxime was most effective in reactivating cholinesterase *in vitro*. Grob & Johns (65) found that the

[illegible]

patients afflicted with myasthenia gravis They recommend the use of these oximes as adjuncts to atropine in the therapy of cholinesterase inhibition, as a means of limiting the need for artificial respiration and intubation.

Fluoride—Publications concerned with the medical and hygienic problems that have arisen in connection with the use of the compounds of fluorine have multiplied in recent years into a vast literature. The prospect of achieving some grasp of the scope and significance of this literature has been improved greatly by the appearance in 1958 of the first book of an annotated bibliography on the occurrence and biological effect of these compounds. A second book which will complete the bibliography of the inorganic compounds will appear within the year, thus making available a major reference work. The compilation of the references and the abstracting of the more important papers was initiated by Campbell & Widner (66) in 1947 The two books which comprise Volume I (Volume II, concerned with the organic compounds, will be forthcoming later) contain some 8700 references and cover the field broadly, but concentrate to some extent on matters of interest in the field of industrial hygiene.

Air pollution.—The efforts of investigators in this country and abroad to delineate certain general or more or less specific effects of air pollution on human health continue vigorously on the two main fronts, namely: (*a*) that of the experimental laboratory, in which the responses of animals or human volunteers to known and controlled conditions are observed and recorded; and (*b*) that of epidemiologic surveys of random or selected populations in which the responses of individuals or groups to specific tests are correlated with specific variables in the atmospheric environment. The extreme difficulties of either of these approaches, with special reference to the relevance of the conditions and reactions under observation, are such that progress is

since the most powerful radar now in use is not capable of exceeding the level of 0.01 watt per sq cm. at a distance of 500 ft. However, an average power output of 600 kw. has been developed, and the use of 1000 kw. is envisioned shortly. The power output of some of the new equipment will certainly attain levels capable of causing biological damage, although the process involved is a simple transfer of energy with only a resultant thermal change.

Investigations indicate that a cumulative effect of some type is exerted upon the lens of the eye following repetitive exposure to subthreshold dosage of energy at the frequency of 2450 Mc. Preliminary observations in which encephalographic responses have been induced in the rabbit by exposure to this type of energy at the frequency of 24,500 Mc. indicate the need for further extensive investigation of the effects of microwaves upon the nervous system.

Miscellany

The trends and contributions in industrial toxicology were reviewed so thoroughly in 1955 and 1956 (62a, 63) as to have obviated the need for an equally comprehensive survey of the field at this time. This is not to suggest that the flow of investigative work has subsided since, but rather that it has undergone little change in direction. A significant trend toward the examination of toxicologic mechanisms and metabolic patterns has developed within a number of laboratories, but the influence of this trend on the literature of the field is not obvious or general.

Boranes.—Among the relatively new problems is that created by the development and use of certain high-energy fuels, among which the boranes (di-, penta- and decaborane) have attracted the attention of toxicologists and, because of the effects sustained by exposed personnel, also physicians. No entirely reliable information has been published as yet concerning either the toxicology or the clinical manifestations which characterize these materials Work is under way, however, and the publication of results is expected soon. It seems fairly well established that any one of these compounds absorbed in sufficient but small dosage, will induce an intoxication of the central nervous system and damage to the liver and kidney Apparently, only an acute form of intoxication has occurred among workmen, and complete recovery is said to have ensued in all instances. The intoxication, as described thus far, has been characterized by irritation of the central nervous system, with confabulation and thickness of speech (convulsions have occurred in a few instances). The liver profile has remained normal, although some increase in cephalin flocculation has occurred. Apparently, the absorption of decaborane results in more insidious and prolonged manifestations than does that of the other boranes.

Insecticides.—New insecticides continue to appear upon the scene. In each instance, new toxicological information is forthcoming as a condition of its use. The efforts being made to develop entirely safe or at least less dangerous

insecticides for specific uses have not been outstandingly successful. On the other hand, the requirements with respect to toxicological information, prior to the introduction of new insecticides, are increasing steadily There are both advantages and disadvantages in this situation, but they add to the impetus toward the discovery of safe yet effective agents.

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Holmes & Robins (64) found that pyridine-2-aldoxime was most effective in reactivating cholinesterase *in vitro*. Grob & Johns (65) found that the former compound, as well as diacetyl monoxime, relieved the generalized weakness induced by the absorption of organophosphorus compounds (those characterized by anticholinergic properties) by normal subjects as well as by patients afflicted with myasthenia gravis They recommend the use of these oximes as adjuncts to atropine in the therapy of cholinesterase inhibition, as a means of limiting the need for artificial respiration and intubation.

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destined to be slow and the publication of results and conclusions, on the part of the critical and cautious, even slower. Progress is being made, however, although little that is new has been published. Among publications of interest is that of Fairbairn & Reid (67) who, in examining data on mortality in relation to indices of visible fog, density of population, and domestic overcrowding, have found significant correlations between death rates from specific respiratory diseases within the age group 45 to 64 in the general population of Great Britain (surveys in 37 different areas) and one or more of the environmental factors under consideration. Examples of such correlations are (*a*) the highly significant relationship of mortality from bronchitis to visible fog, without regard to sex; (*b*) the significance of both fog and population density in relation to the mortality from pneumonia among males, but not to the mortality from overcrowding among persons of either sex; (*c*) the irrelevancy of fog with respect to deaths from tuberculosis, but the strong correlation between population density and deaths from this disease; and (*d*) the highly significant correlation between cancer of the lung (in both sexes) and population density, without any demonstrable relationship between this disease and the other two variables. Other details of these significant investigations should be sought in the publication. It should be recognized that this situation in Great Britain, whether or not it is unique, is not duplicated in the United States with respect to the mortality from bronchitis nor, as a general rule, from the aspect of atmospheric conditions. These facts do not lessen the importance of these observations, but they illustrate the need for caution in arriving at generalizations.

THE GENERAL ENVIRONMENT AND RESPIRATORY DISEASE

That the air around us may contain myriads of microorganisms in suspended droplets was demonstrated convincingly by the researches of Wells (68) In his monograph Wells discusses the physics and physical chemistry of droplets and droplet nuclei, and the biology of infection by droplet-nuclei.

Our awareness of a large spectrum of viral respiratory disease has grown over the last 15 years. Dingle (69), after an analysis of his experiences with soldiers during World War II, concluded that a host of respiratory diseases are caused by viral organisms other than the influenza virus, and that many of these are intermediate in severity between the common cold and the atypical pneumonias.

With the development of techniques for the identification and study of viral organisms, and the concomitant increase in the study of the serology of patients with respiratory illness, hitherto unknown relationships between viral organisms and respiratory illness have come to light Rowe, Huebner & Bell (70) have summarized the state of our knowledge of the adenoviruses. Hilleman (71) has discussed the epidemiology of adenoviral respiratory infections among military recruits He included the results of his use of a formalin-killed vaccine prepared from infected cultures of monkey renal epithelium This vaccine, containing viruses of both types 4 and 7, appeared

to be highly protective at the end of one week after its administration. The frequency of adenoviral infections in civilian populations has been investigated by Jordan (72, 73). Grieble *et al.* (74) have studied a group of 122 adults with acute respiratory infection to determine the etiologic agent so far as possible. Their results indicate that, while the greater proportion of acute respiratory illness of known etiology was viral in origin, only a small proportion of such viral disease was due to the adenoviruses. It would seem, therefore, that immunization of civilian populations against the adenoviruses could hardly be expected to effect much reduction in the incidence of acute respiratory disease in such populations.

Investigations relating to the environmental control of droplet-borne infection have been reported by Wells (68). Air hygiene may be achieved by adequate ventilation, ultraviolet irradiation, and chemical decontamination with glycol vapor. Despite the efficacy of these measures when applied under appropriate conditions in any given environment, such as the factory, the office, the school room, or the hospital ward, the effect of "checkerboarding," or of moving from one environment to another, merely permits a greater proportion of the seeding of respiratory infection to occur in uncontrolled surroundings when susceptible persons move back and forth between controlled and uncontrolled environments. None of these measures can be counted on to exert an important influence upon the incidence of respiratory disease unless the populations concerned are under appropriate control.

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